

# PHD DAY

## HEALTH

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**PROGRAMME & ABSTRACTS**  
23 JANUARY 2015



AARHUS  
UNIVERSITY

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# PHD DAY 2015 PROGRAMME

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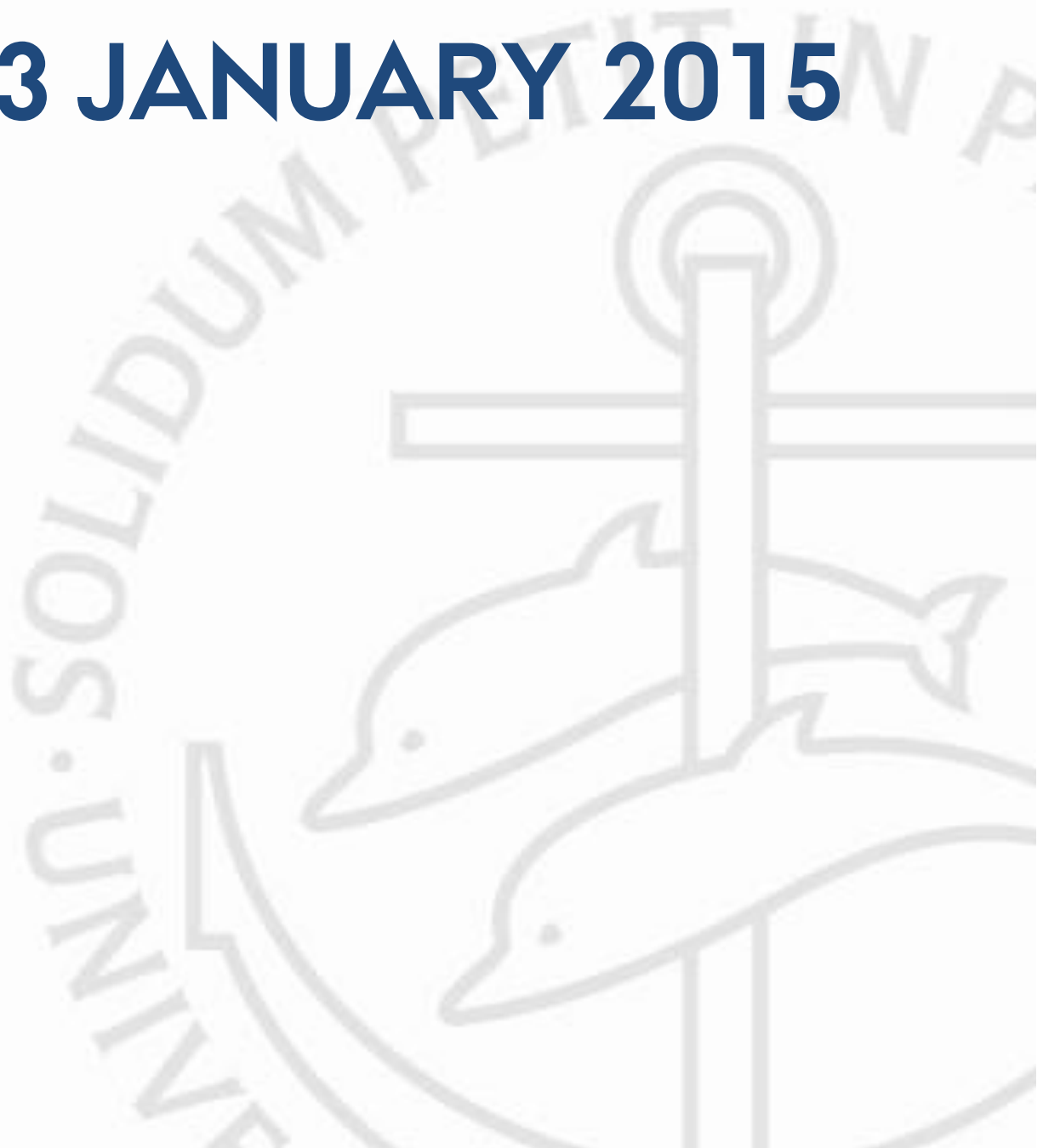
- 8.30 Welcome  
*Professor Lise Wogensen Bach, Vice dean and Head of Graduate School*
- 8.40 Welcome and today's program  
*Alexander Juhl Andersen, Co-chairman of the PhD Association*
- 8.45 Fogh-Nielsen Prize competition  
*Chaired by Professor Søren Moestrup, chairman of the Fogh-Nielsen board*
- 9.30 Coffee/tea and fruit break  
*The Lakeside auditorium*
- 9.45 Oral presentations  
*The Lakeside auditorium*
- 11.15 Break
- 11.30 Poster presentations  
*Bartholin (build. 1241), Anatomy (build. 1230) and the Lakeside Auditorium*
- 12.45 Lunch /poster viewing  
*Bartholin (build. 1241), Anatomy (build. 1230) and the Lakeside Auditorium*
- 13.30 "Academic doping", panel debate  
*Panel participants: Professor Kirsten Ohm Kyvik, Professor Jørgen Frøkiær  
Associate Professor Ask Vest Christiansen and Professor Eskild Petersen*
- 15.00 Coffee/tea and cake break  
*The Lakeside auditorium*
- 15.15 "Diligence, Deception and Fraud", key note lecture  
*Morten Staberg, Pediatric specialist, MD*
- 16.00 Poster and oral awards  
*The Lakeside Auditorium*
- 16.45 Closing remarks  
*Professor Lise Wogensen Bach, Vice dean and Head of Graduate School*
- 18.30 Dinner and awards ceremony for the JCD and the Fogh Nielsen prizes  
*Centralværkstedet  
Festive speech by Professor Ole Bækgaard Nielsen*



Aarhus University  
Graduate School of Health

# **PHD DAY**

## **23 JANUARY 2015**



# Practical Information

- Posters should be hung up between 4.30pm and 8pm on January 22<sup>nd</sup> or between 7.30am and 8am on January 23<sup>rd</sup>. All posters must be taken down before 3.00 pm
- Oral presenters for sessions O1-O5 must meet in the auditorium concerned between 7.30am and 8:00am on January 23<sup>rd</sup> to save their presentation onto the auditorium hard disk.
- Lunch is served at the Lakeside Lecture Theatre and at the poster viewing areas in the Bartholin Building and at Anatomy.

**Oral session 1:** Lakeside Lecture Theatres, Per Kirby Auditorium

**Oral session 2:** Lakeside Lecture Theatres, Merethe Barker Auditorium

**Oral session 3:** Lakeside Lecture Theatres, Eduard Biermann Auditorium

**Oral session 4:** Lakeside Lecture Theatres, Jeppe Vontilius Auditorium

**Oral session 5:** Bartholin building, Auditorium 1

**Postersession 1-7 :** Lakeside Lecture Theatres, William Scharff

**Postersession 8-28:** Bartholin building, Auditorium 2, 3, 4, studyroom, gardenroom and Hall.

**Postersession 29-38:** Anatomy (building 1230): Hall and Kollokvieroom 1

## Organizing committee:

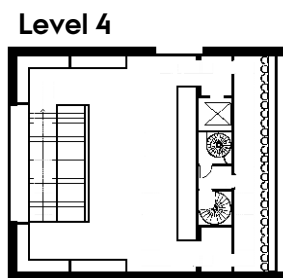
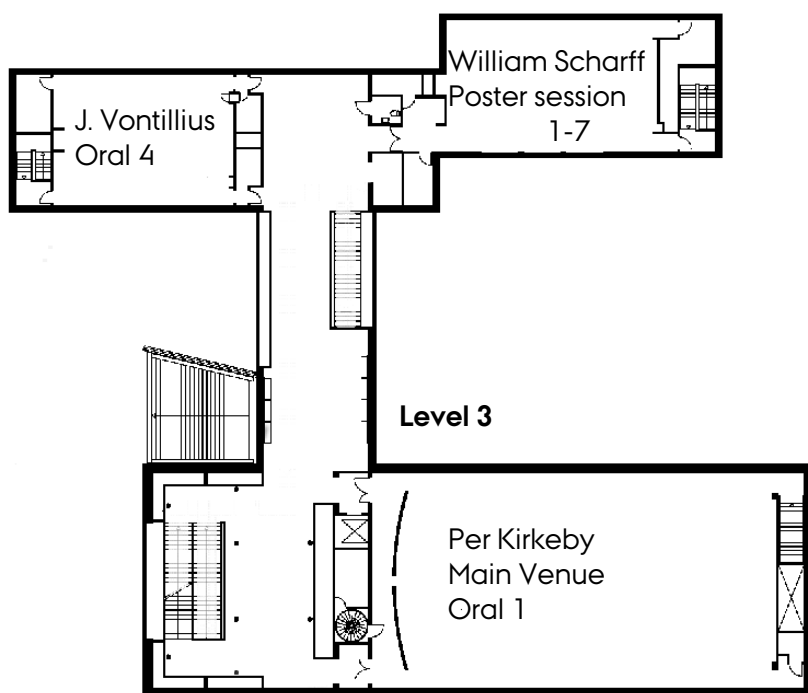
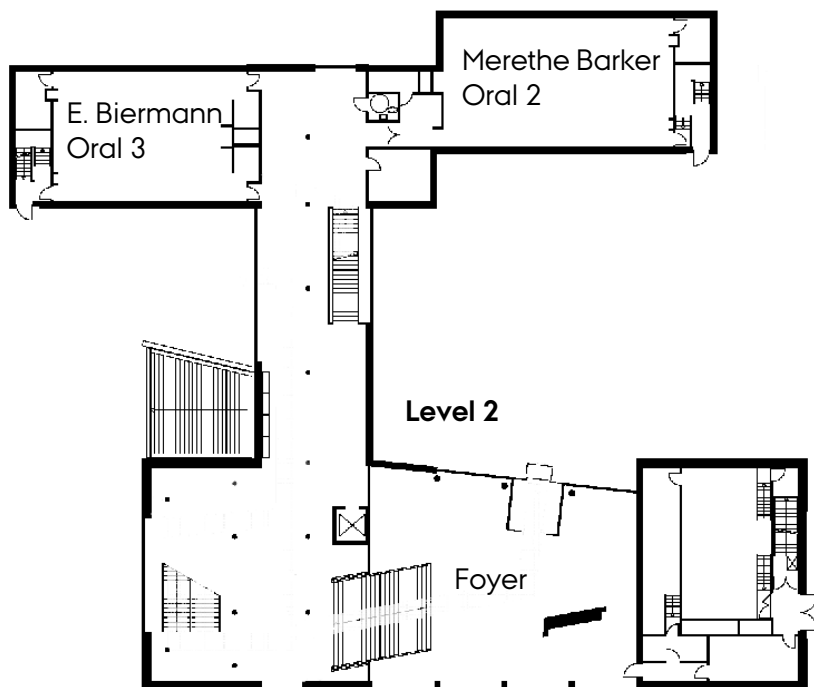
- Helle Prætorius, Professor mso, DrMedSc, Department of Biomedicine, Chairman
- Martin Roelsgaard Jakobsen, Ass. Professor, Department of Biomedicin
- Jakob Østergaard, Postdoc, Department of Clinical Medicine
- Alexander Juhl Andersen, PhD student, Department of Clinical Medicine
- Kasper Pryds, PhD student, Department of Clinical Medicine
- Anne-Mette Haase PhD student, Department of Clinical Medicine
- Nanna Sophie Brinck-Jensen, PhD student, Department of Clinical Medicine
- Maryam Ardalan, PhD student, Department of Clinical Medicine
- Rikke Hjortebjerg, PhD student, Department of Clinical Medicine
- Emilie Glavind, PhD student, Department of Clinical Medicine
- Jennie Maria Strid, PhD student, Department of Clinical Medicine
- Sigrid Salling Árnadóttir, PhD student, Department of Clinical Medicine
- Johan Arendt, PhD student, Department of Clinical Medicine
- Sidsel Lindberg Tefre, PhD Administration
- Birgitte Rosenvind Eriksen, PhD Administration

## Social media :

Facebook: Phd Association Health

Twitter: #auphd15





#### Bartholin Building

Oral 5

Poster session 8-28

#### Anatomy

Poster session 29-38

# Academic Doping

On behalf of the PhD-Association, the organising committee welcome all students, faculty members and distinguished guests to the PhD Day 2015.

The topic of this year's programme is *academic doping*, which is also the theme for our panel debate. We hope to evoke both strong opinions and contemplation on the motives for scientific publications and relevant ethic considerations. Is it possible to have a scientific career, while keeping to the straight and narrow? We will hear the opinion from this year's panel consisting of Head of Institute, Institute of Regional Health Services Research, SDU, Professor Kirsten Ohm Kyvik; Chair of The Danish Council for Independent Research | Medical Science, Professor Jørgen Frøkiær; Lecturer Ask Vest Christiansen and Editor-in-Chief, International Journal of Infectious Diseases, Professor Eskild Petersen. This line-up should guarantee a lively debate on the highest level. As something new, the audience in the auditorium is invited to contribute directly with comments and questions on debaters via social media.

The choice of this year's Key Note Lecturer is Morten Staberg, who will tackle ethics in medical practice and medical science.

A warm thank goes to all those who have taken their time to participate and help making this PhD Day a leading event.

Professor MSO Helle Prætorius  
Chairman of the Organizing Committee  
Health, Aarhus University

Professor MSO Lise Wogensen Bach  
Vice-dean and Head of Graduate School  
Health, Aarhus University

Professor Allan Flyvbjerg  
Dean  
Health, Aarhus University

PhD fellow Alexander Juhl Andersen  
Co-chairman of the PhD association  
Health, Aarhus University

# The Keynote Lecture

## Morten Staberg, Pediatrician



Dr. Staberg is owner of the consultant business Staberg.dk and co-founder of the education company Staberg-Vesterdahl. He earned his MD degree at Copenhagen University and has specialized in pediatrics at Hvidovre Hospital, Glostrup Hospital and Herlev Hospital in the Capitol Region of Denmark. He has worked with neglected, violently and sexually abused children at Center for Social Pediatrics and Center for Sexually Abused Children at Herlev Hospital and Rigshospitalet, respectively.

Dr. Staberg often uses humor to address serious problems. He is a columnist in the Danish medical journal Ugeskrift for Læger, and has drawn the attention of the Danish MDs and researchers to safeguard their reputation. He also runs a Facebook debate forum called Læger for Danish MDs – it has more than 1.100 members.

Dr. Staberg has actively participated in the public debate regarding the quality, efficiency and safety of care in Danish hospitals. In 2011, he united more than 2.500 Danish MDs in order to end the expensive and inefficient collaboration with the American company, Joint Commission, in the Capitol Region, and to obtain proper budget funding to improve the quality of IT in the Danish health care sector.

Furthermore, Dr. Staberg continuously takes a stand in defending children's rights and strongly believes in the individual's right to choose their own faith and sexuality - regardless of gender. He actively opposes non-medical circumcision of both girls and boys and trusts that Denmark will be the first country in the world to give children of both genders equal rights to intact bodies.

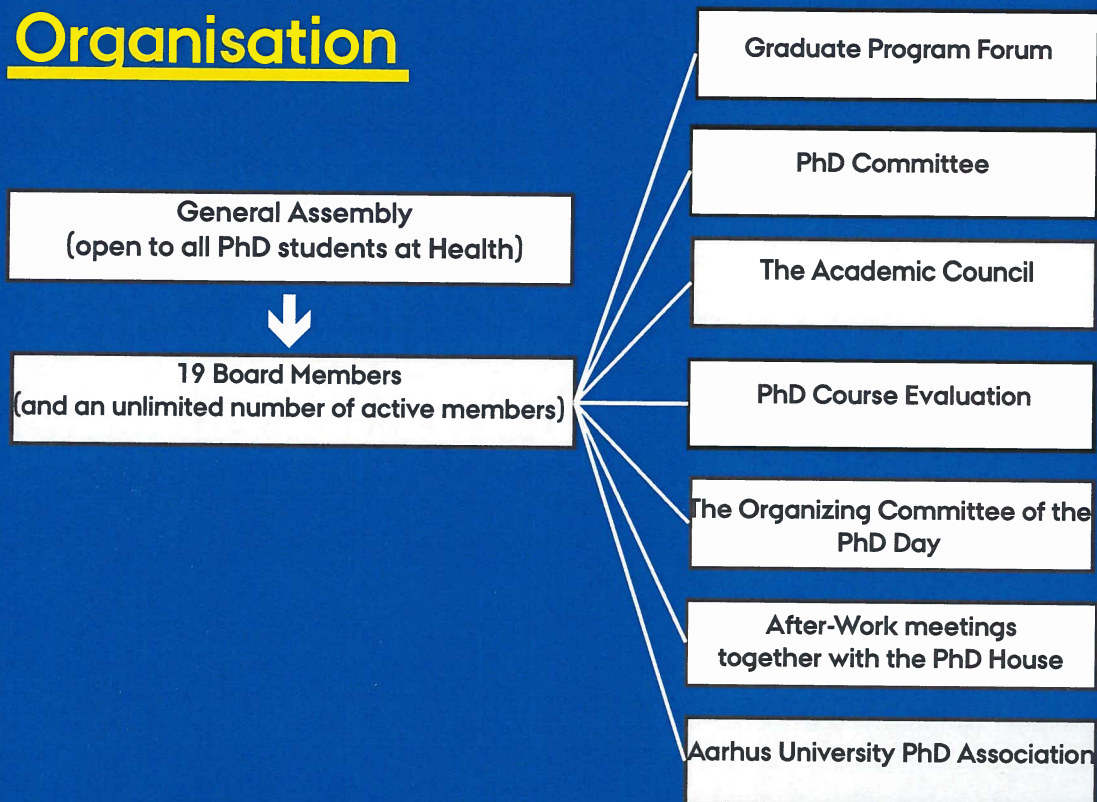
Unfortunately, as a cancer patient, Dr. Staberg has personal experience from both the Danish and American health care system. It has made a major impact on his view of the different aspects of patient care and how we prioritize in Denmark. He is currently cooperating with the Danish radio station P1 concerning a broadcast on this issue. He also does inspiring talks and lectures about the Danish health care system together with the comedian Geo, who has also suffered from cancer.

Dr. Staberg has only once won any kind of price or award. More than 20 years ago, he was voted Most Improved Player of the Year on his college tennis team. Yet, he somehow still manages to believe that life is not just about participating.

# Phdassociation.dk

*The PhD association for all PhD students at the  
Faculty of Health*

## Organisation



**We aim to create better education and better  
conditions for PhD students at the  
Graduate School of Health!  
Join us on Facebook at Phd Association Health!**



**Everyone is welcome!**



# Student counsellor for PhD students

*Surviving you dissertation*

*From time to time it is more than a book title.*

In the knowledge that studying for a PhD can be an overwhelming challenge, then Health has established a student counsellor for PhD students. What would you answer if I asked:

*Is it difficult to plan your daily work?*

*Are things not working?*

*Is it hard to collaborate with your supervisor?*

*Do you find your situation as a PhD student difficult or unsatisfactory?*

I am always an interested listener. As PhD student counsellor I am a professional interlocutor. Conversations with me are confidential and anonymity is promised. It is not an alternative to the professional research supervision. By means of conversations, the counsellor can help students become aware of what they perceive as difficult and why. This is done in close collaboration with the Secretary of The Graduate School of Health if the process related issues have administrative elements. The intention is to help PhD students gain clarity, come to terms with their situation. It is also to help them to see other opportunities, if they experience personal problems or other difficulties related to the process of working and studying as a PhD student. The counsellor can also assist students to make competent decisions.

**You are always welcome to contact the PhD student counsellor!**

**Sometimes sooner is better than latter - no problem is too small for a talk.**

Personal contact: Sanne Angel

phdstudievejleder@sun.au.dk

Phone: 871 67889

# PhD - and then what?

Do you wish to continue research after finishing your PhD?

## **Think about joining the Danish Society for Postdoctoral Health Research**

The Society was founded in 2012 by Health Professionals who found it challenging to combine clinical work and research. The purpose of the Society is to promote, improve, and develop opportunities to do health research after being awarded a PhD- or DrMedSc-degree.

We focus on integrating clinical work with research.

### **Mission statement**

The Danish Society for Postdoctoral Health Research works to provide:

- the opportunity to network with other postdoctoral research fellows
  - education and training including  
Symposia, workshops, after-work-meetings and access to postdoctoral courses
- access to IT infrastructure: email service, server for data back-up, software licenses and IT- support in general
- a liaison between postdoctoral researchers and the university
- a collective voice for issues that are relevant and of interest to postdoctoral researchers towards institutions e.g. the Danish Health and Medicines Authority, Danish Regions, the Danish Agency for Science, Technology and Innovation, different Unions, and the Hospital Board of Directors .
  - social events

**Everyone with a PhD or DrMedSc in Health Sciences can join the Society.**





# AU **LIBRARY** HEALTH SCIENCES

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## THE LIBRARY IS HERE TO HELP

- Access to relevant literature
- Information about:
  - Tips and tricks for PubMed, Embase, Scopus, and Cinahl
  - Citation searches in Scopus and Web of Science
  - Alerts from your favourite journals
  - Reference Tools – courses and support for EndNote and RefWorks
  - Bibliometrics and Research Evaluation; e.g. Bibliometric Research Indicator (BFI), Journal Impact Factor, and H-index
  - Copyright and Open Access
- Individual support and help for literature search designed for your specific project
- Regular PhD courses 'Literature Search in Medical Databases'

### **AU Library, Health Sciences**

Victor Albeck Building

Vennelyst Boulevard 4

DK-8000 Aarhus C

Tel. +45 8946 2362

[sundhedsvidenskab@statsbiblioteket.dk](mailto:sundhedsvidenskab@statsbiblioteket.dk)

### **Opening Hours**

Monday – Friday 9 a.m. – 6 p.m.

# GERDA

AU ALUMNI COMMUNITY NAMED AFTER THE FIRST ALUM



## GERDA WHO?

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Gerda, our online community for alumni, is named in honor of the first alumni from AU who graduated in 1935.

Today, the alumni community is a central meeting point for alumni, students, faculty and staff, which sets the perfect scene for discovering old and new connections, staying up to date on events and other networking offers.

It's free to be a member – all you have to do is activate your profile at [gerda.au.dk](https://gerda.au.dk).



AARHUS  
UNIVERSITY  
ALUMNI

[gerda.au.dk](https://gerda.au.dk)



# It's your **talent** – It's your **career** – It's your **choice!**

Do you know which career path to choose when finishing your PhD?  
Do you know which specific competences companies are interested in regarding PhD students from Health? Are you aware of your many opportunities?

If these are some of the questions you ask yourself, we may be able to guide you:

Get a mentor from the business community and increase your network outside of academia

Individual feedback on career paths, applications and CVs

AU Job & Project Bank

Information on career opportunities

Career events

Contact the AU Career Advisory Panel and get feedback from experts within your field

Do not hesitate to contact us. We look very much forward to meeting you.

**READ more about our services at** [phd.au.dk/career](http://phd.au.dk/career)

AU **CAREER**  
PHD



AARHUS UNIVERSITY

Best regards,

**Vibeke Broe**

PhD Career Consultant

Mobile: 2942 6029

Email: [vibr@au.dk](mailto:vibr@au.dk)

[phd.au.dk/career](http://phd.au.dk/career)

## International Academic Staff Services (IAS) at International Centre

In close collaboration with AU Human Resources, the International Academic Staff Services (IAS) helps foreign researchers (incl. PhD students) and their families through the practical challenges tied to living in Denmark. As part of this, the unit operates a service desk and a website ([www.ias.au.dk](http://www.ias.au.dk)) primarily for international PhD students and academic staff admitted to AU.

IAS assists international staff and PhDs through social and cultural events. The unit counsels about issues of relevance for the international PhD students and their family, incl. job for the spouse and international schools and nurseries. The unit also provides some information about practicalities for students planning a period abroad.

Furthermore, IAS assists international staff and PhD students with paperwork and practical challenges during their stay in Denmark, e.g. health insurance and extension of residence and work permits. The IAS service desk for PhD students is open Monday – Friday 10am-2pm at the International Centre.

To make the transition to Denmark as easy as possible IAS encourage new internationals to participate in the introductory events. The AU Introduction Day gives a general introduction to AU as an organisation and takes place every other month. Additionally, twice a month IAS organises Getting Started in Denmark which provides important on-arrival orientation and registration for newly arrived international PhD students and researchers, see <http://ias.au.dk/gettingstarted/>.

Lastly, IAS helps arranging social activities for staff and their families through the University International Club (UIC). For further information, visit [www.au.dk/uic](http://www.au.dk/uic).

## PhD House Activity Group

The PhD House Activity Group is an interdisciplinary group of volunteer PhDs and postdocs that organises a wide range of social and academic events primarily aimed at both Danish and international PhDs and post docs. The group is working to enhance the junior researchers' environment at Aarhus University and is always looking for new enthusiastic members.

## The PhD House

The PhD House is located in the Dale T. Mortensen Building (International Centre). The PhD House offers a combination of administrative services, lecture rooms for PhD courses on transversal skills and Dale's Café offering quality coffee, sandwiches and a wide selection of beers. Furthermore, the PhD associations have the possibility to use the facilities in the PhD House for events.

The PhD House is, thus, a focal point for national and international PhD students to meet both professionally and socially.

## The International Centre

AU International Centre is located in the Dale T. Mortensen Building (Høegh-Guldbergs Gade 4), including IAS and the housing department dealing with housing matters for international PhD students. IC Dormitory for international PhD students is also part of the Dale T. Mortensen Building.



# Do you need **funding** for your research?



- The Health Team at The Research Support Office can **help you tailor a competitive application and make a realistic budget.**
- Our database [www.ResearchFunding.Net](http://www.ResearchFunding.Net) will help you **find funding opportunities.**

**Research Support Office — Proposal Development**

Aarhus University & Aarhus University Hospital

[www.au.dk/fse](http://www.au.dk/fse)

## PHENOTYPING POSSIBILITIES AT AARHUS UNIVERSITY

Characterisation of living animals, phenotyping, is an important component of scientific and medical research. Exciting and ground breaking research involving animals take place at Aarhus University. The research areas span wide and are very diverse in nature.

### FACILITIES

Research is carried out at the departments in the faculties of Health and Science and Technology in the Science Park and at Aarhus University Hospitals as well as other associated research facilities (e.g. Foulum and Påskehøjgård). Specific research facilities for laboratory animals available at all sites.

### HOW MAY PHENOTYPING HELP YOUR RESEARCH PROJECT?

Researching complex reactions in living systems necessitates and requires the use of experimental animals. Animal research is one vital strand of medical research that together with *in vitro* experimentation ensures that research findings are more robust and reliable. Thus, phenotyping of live animals contribute greatly to the understanding of diseases, their development and mechanisms as well as the development of more specific and effective treatments of diseases and debilitating conditions. Phenotyping can be time consuming and resource-intensive and therefore a resource- and competency catalogue has been built.

### RESOURCE AND COMPETENCE CATALOGUE

A dedicated website for phenotyping act as a resource- and competency catalogue for researchers at Aarhus University. It provides an overview of existing phenotyping possibilities and expertise that is available at Aarhus University. The website describes each phenotyping test in terms of measurable parameters, available equipment, location of equipment and provides contact information to a scientist who is a specialist in the specific research area. The website can be accessed at: (<http://biomed.au.dk/forskning/core-faciliteter/faenotyping/phenotyping/>)

**For further information about phenotyping activities at Aarhus University contact Project Coordinator for Phenotyping, Ellen Villadsen: E-mail:evil@fi.au.dk or Tel: 21551544.**



Danish Diabetes Academy was established in 2012.

The overall aim of the Academy is to ensure Denmark's leading position within diabetes research in future

In collaboration with the Danish universities and university hospitals, the Academy aims to offer world-class educational activities such as PhD courses and seminars with both basic and clinical diabetes research.

The Academy also aims at acting as a networking platform between national and international diabetes researchers. The networking part will be initiated through workshop activities, annual days and Post Doc Club meetings.

The Academy will allocate 140 grants to excellent PhD students and Post Doc fellows. All available grants will be posted in full and open competition.

For further information about

- PhD courses, seminars and other educational activities
- Networking activities
- Grants

Please visit our website: [www.danishdiabetesacademy.dk](http://www.danishdiabetesacademy.dk) ,  
join us on Facebook (<https://www.facebook.com/danishdiabetesacademy/timeline> ) or  
LinkedIn ([https://www.linkedin.com/company/danish-diabetes-academy?trk=top\\_nav\\_home](https://www.linkedin.com/company/danish-diabetes-academy?trk=top_nav_home) )

Sincerely

Tore Christiansen  
Managing Director

## Session chairmen

O1	Alma B. Pedersen & Line Flytkjær Jensen
O2	Jeppe Prætorius & Rakel Fuglsang Johansen
O3	Bent Deleuran & Mads Skipper
O4	Frank de Paoli & Katherina Farr
O5	Karin Lykke-Hartmann
P1	Vladimir Matchkov & Kasper Hansen
P2	Lars Maagard Andersen, Stine Hald & Nis Pedersen Jørgensen
P3	Lars Bolund & Mette Lausten Hansen
P4	Robert Fenton, Nikolaj Rittig & Zahra Nochi
P5	Natalya Fedosova, Randi Heidemann Gottfredsen & Anna Budtz-Lilly
P6	Mai Marie Holm & Veerle Paternoster
P7	Johan Palmfeldt & Kristian Krogh
P8	Torsten Bloch Rasmussen & Anne Dorte Blankholm
P9	Elise Røge Hedegaard & Helene Tilma Vistisen
P10	Donna Briggs Bødtkjær & Christian Bo Poulsen
P11	Torbjørn Brøgger
P12	Jens Leipziger & Sara Heebøll
P13	Marianne Uhre Jakobsen & Maria Charlotte Steffensen
P14	Peter Bross, Navid Sahebekhtiari & Anne Kristine Amstrup
P15	Niels H Birkebæk, Christian Bjerregaard Olesen & Christian Lottrup
P16	Irene Dige & Maj Høygaard Nicolaisen
P17	Efe Levent Aras & Sepp de Raedt
P18	Casper Foldager & Mette Winther
P19	Yonglun Luo & Aida Solhøj Hansen
P20	Morten Nielsen & Sofie Christiansen
P21	Carmela Matrone & Gro Helen Dale
P22	Jens R. Nyengaard & Maryam Ardalan

P23	Simon Fristed Eskildsen & Abhishek Kumar
P24	Erik Johnsen & Anette Riisgaard Ribe
P25	Mads V Sørensen, Lu Xing & Louise Bill
P26	Morten Ladekarl & Anne Vestergaard
P27	Tine Engberg Damsgaard, Jakob Kristian Jakobsen & Maja Ølholm Vase
P28	Michael R. Horsman & Søren Haack
P29	Klaus Krogh, Michał Świtnicki & Jill Rachel Mains
P30	Niels Gregersen & Lea Hougaard Pedersen
P31	Uffe Birk Jensen & Moslem Ranjbar
P32	Marianne Lisby & Camilla Hoffmann Merrild
P33	Simon Tilma Vistisen & Cathrine Carlsen Bach
P34	Charlotte Ulrikka Rask & Mette Kjærgaard Nielsen
P35	Christiane Beer & Peter Bondeven
P36	Reimar W. Thomsen & Sebastian Ranzi Kotze
P37	Tove Christensen, Kathrine Hansen & Thomas Nordstrøm Kjær
P38	Per Höllsberg, Gitte Julie Christensen & Esben Axelgaard

## Session overview

### Fogh Nielsen

Tue Wenzel Kragstrup. IL-20 AND IL-24 LINK RHEUMATOID FACTOR POSITIVITY AND BONE DESTRUCTION VIA THE IL-22R SUBUNIT IN RHEUMATOID ARTHRITIS

Henry Jensen. DIAGNOSTIC INTERVALS AND TUMOUR STAGE BEFORE AND AFTER IMPLEMENTATION OF STANDARDISED CANCER PATIENT PATHWAYS

Konstantin Kazankov. THE MACROPHAGE ACTIVATION MARKER SOLUBLE CD163 IS A BIOMARKER OF LIVER DISEASE SEVERITY

### Oral session 1

Chairmen: Alma B. Pedersen & Line Flytkjær Jensen (PhD student)

- O01.01      Xiaoqin Liu. MATERNAL ANTIDEPRESSANTS USE DURING PREGNANCY AND ASTHMA IN THE OFFSPRING: A POPULATION-BASED COHORT STUDY
- O01.02      Jette Pedersen. DOES POST DISCHARGE NUTRITIONAL SUPPORT TO MALNOURISHED GERIATRIC PATIENTS AFFECT ADL FUNCTION?
- O01.03      Charlotte Simonj. HEART- SHAKING TRANSITIONS DURING CARDIAC REHABILITATION - A PHENOMENOLOGICAL-HERMENEUTIC STUDY OF PATIENTS' EXPERIENCES
- O01.04      Nanna Rolving Rasmussen. DOES A PREOPERATIVE COGNITIVE-BEHAVIOURAL INTERVENTION AFFECT DISABILITY, PAIN BEHAVIOUR, PAIN AND RETURN TO WORK THE FIRST YEAR AFTER LUMBAR SPINAL FUSION?
- O01.05      Mette Ladefoged. RETINAL VASCULAR INSULIN SIGNALING DIABETIC RETINOPATHY
- O01.06      Ingeborg Hedegaard Kristensen. ARE HEALTH VISITORS' OBSERVATIONS OF EARLY PARENT-INFANT INTERACTIONS RELIABLE? A CROSS-SECTIONAL STUDY

### Oral session 2

Chairmen: Jeppe Prætorius & Rakel Fuglsang Johansen (PhD student)

- O02.01      Anne Cathrine Sønderstgaard Thorup. VINTAGE VEGETABLES IMPROVE THE HEALTH STATUS OF TYPE 2 DIABETICS WHEN COMPARED TO EQUIVALENT MODERN VEGETABLES.
- O02.02      Casper Kornbech Larsen. REDUCED RENAL K<sup>+</sup>EXCRETION WITH COMPENSATORY HYPERALDOSTERONISM IN K<sub>CA</sub>1.1 CHANNEL BETA<sub>2</sub>-SUBUNIT KO MICE
- O02.03      Kirstine Kobberøe Søgaard. SPLANCHNIC VENOUS THROMBOSIS IS A MARKER OF CANCER AND A PROGNOSTIC FACTOR FOR CANCER SURVIVAL
- O02.04      Jakob Dal. INCIDENCE AND LATE PROGNOSIS OF ACROMEGALY IN DENMARK: PRELIMINARY DATA
- O02.05      Marie Krarup Schrøder. DURATION OF USE AND SAFETY OF DESMOPRESSIN IN BEDWETTING PATIENTS: RESULTS FROM 8-YEARS REGISTRATION OF 214,220 DESMOPRESSIN PRESCRIPTIONS TO 40,596 INDIVIDUAL USERS



- O02.06      Andreas Buch Møller. ULK1 PHOSPHORYLATION IS ALTERED BY PHYSICAL EXERCISE, FASTING, AND INSULIN IN HUMAN SKELETAL MUSCLE

### Oral session 3

Chairmen: Bent Deleuran & Mads Skipper (PhD student)

- O03.01      Mikkel Tøttrup. BONE, SUBCUTANEOUS TISSUE AND PLASMA PHARMACOKINETICS OF CEFUROXIME IN TOTAL KNEE REPLACEMENT PATIENTS - CONTINUOUS VERSUS SHORT-TERM INFUSION
- O03.02      Ane Langkilde-Lauesen Nielsen. TRIM21 IN PSORIASIS
- O03.03      Karen Toftdahl Bjørnholdt. LOCAL INFILTRATION ANALGESIA VERSUS CONTINUOUS INTERSCALENE BRACHIAL PLEXUS BLOCK FOR SHOULDER REPLACEMENT PAIN: A RANDOMIZED CLINICAL TRIAL
- O03.04      Lars Bo Petersen. NEUROSENSORIC DISTURBANCES AFTER SURGICAL REMOVAL OF THE LOWER THIRD MOLAR BASED ON EITHER PANORAMIC IMAGING OR CONE BEAM CT SCANNING (CBCT). A RANDOMIZED CONTROLLED TRIAL
- O03.05      Jeppe Lange. VALIDITY OF HIP PROSTHESIS RELATED INFECTION DIAGNOSIS AND PROCEDURE CODES IN ADMINISTRATIVE REGISTRIES. A CROSS-SECTIONAL STUDY IN THE DANISH NATIONAL PATIENT REGISTRY FROM 2003 TO 2008
- O03.06      Line Raaby Steenberg. CHANGES IN MRNA EXPRESSION PRECEDE CHANGES IN MIRNA EXPRESSION IN LESIONAL PSORIATIC SKIN DURING TREATMENT WITH ADALIMUMAB

### Oral session 4

Chairmen: Frank de Paoli & Katherina Farr (PhD student)

- O04.01      Simon Gabriel Comerma Steffensen. ROLE OF SK<sub>3</sub>CHANNELS IN ERECTILE FUNCTION IN MICE
- O04.02      Lone Winther Lietzen. AUTOIMMUNE DISEASES AND BREAST CANCER RECURRENCE: A DANISH NATIONWIDE PROSPECTIVE COHORT STUDY
- O04.03      Johannes Martin Schmid. PRE-TREATMENT COMPONENT SPECIFIC IGE DETERMINES THE IGG4 RESPONSE UNDER THE UPDOSING PHASE OF SUBCUTANEOUS IMMUNOTHERAPY WITH TIMOTHY GRASS POLLEN EXTRACT
- O04.04      Niels Bjerregård Matthiesen. CONGENITAL HEART DISEASE AND HEAD CIRCUMFERENCE AT BIRTH: A DANISH POPULATION-BASED COHORT STUDY OF CHILDREN WITH DOWN SYNDROME
- O04.05      Ninna Aggerholm-Pedersen. THE INFLUENCE OF HYPOXIA ON SARCOMA PATIENT'S RESISTANCE TO CHEMOTHERAPY
- O04.06      Søs Ann Christine Neergaard-Petersen. HYPERGLYCAEMIA IS ASSOCIATED WITH A REDUCED ANTIPLATELET EFFECT OF ASPIRIN IN PATIENTS WITH CORONARY ARTERY DISEASE

## Oral session 5

Chairmen: Karin Lykke-Hartmann

- O05.01 Henrique Fernandes. STRUCTURAL BRAIN CONNECTIVITY FINGERPRINTING AS A NEW PRE-SURGICAL TOOL FOR DEEP BRAIN STIMULATION TARGET DISCOVERY
- O05.02 Anders Riisager. EFFECTS OF THE PKC-INDUCED PHOSPHORYLATION ON THE FAST- AND COMMON GATING OF THE MUSCLE SPECIFIC CLC-1 CHLORIDE CHANNEL
- O05.03 Gitte Bundgaard Christiansen. THE ROLE OF THE POSTSYNAPTIC RECEPTOR SORCS3 IN SYNAPTIC PLASTICITY AND SYNAPTIC TRANSMISSION
- O05.04 Baris Isak. INVOLVEMENT OF A-BETA SENSORY FIBRES IN AMYOTROPHIC LATERAL SCLEROSIS
- O05.05 Janne Kærgård Mortensen. ALL-CAUSE 30-DAY MORTALITY RELATED TO POST-STROKE ANTIDEPRESSANT TREATMENT
- O05.06 Christina Sølvsten. NEURONAL EPIGENETIC ALTERATIONS INDUCED BY PHYSICAL EXERCISE

## Poster session 1

Chairmen: Vladimir Matchkov & Kasper Hansen (PhD student)

- P01.01 Mia Hammer Holck. CAN ROTEM® BE USED IN PATIENTS RECEIVING ANTITHROMBOTIC THERAPY?
- P01.02 Simon Graff. LONG-TERM RISK OF ATRIAL FIBRILLATION AFTER THE DEATH OF A SPOUSE: A NATIONWIDE POPULATION-BASED CASE-CONTROL STUDY
- P01.03 Thomas Lyngaa. VARIATION OF INTENSIVE CARE UTILIZATION AT THE END-OF- LIFE IN PATIENTS DYING FROM CHRONIC NON-CANCER DISEASE VERSUS CANCER: A NATIONWIDE CROSS-SECTIONAL STUDY
- P01.04 Anne Katrine Wulff Nielsen. IS HAEMOSTASIS IMPAIRED IN CARDIAC ARREST PATIENTS DURING THERAPEUTIC HYPOTHEMIA?
- P01.05 Sidse Høst Pahu. THROMBOHPILIA IS NOT MORE PREVALENT IN YOUNG PATIENTS WITH ISCHEMIC STROKE THAN IN THE GENERAL POPULATION
- P01.06 Emil Vibede. THE EFFECT OF FRESH FROZEN PLASMA IN CRITICALLY ILL PATIENTS
- P01.07 Jacobina Kristiansen. THE EFFECT OF REMOTE ISCHAEMIC PRECONDITIONING ON CLOT FORMATION AND DEGRADATION
- P01.08 Nina Rise. THE EFFECT OF REMOTE ISCHEMIC PRECONDITIONING ON PLATELET FUNCTION AND PLATELET TURNOVER
- P01.09 Musa Kaya. THE EFFECT OF CHANGES IN PROSTAGLANDIN AND NO LEVELS ON DIAMETER CHANGES IN RETINAL VESSELS DURING HYPOXIA

- P01.10 Lisa Grønbaek Nielsen. DOES BMI MODIFY THE ASSOCIATIONS BETWEEN HBA<sub>1c</sub>, CARDIOVASCULAR EVENTS AND ALL-CAUSE MORTALITY AMONG PEOPLE WITH TYPE 2 DIABETES?

## Poster session 2

Chairmen: Lars Maagard Andersen, Stine Hald (PhD student) & Nis Pedersen Jørgensen (PhD student)

- P02.01 Lars Bossen. THE EFFECT OF NON-SELECTIVE BETA-BLOCKERS ON MORTALITY IN CIRRHOTIC PATIENTS WITH OR WITHOUT REFRACTORY ASCITES
- P02.02 Anne Sofie Hansen. BLOOD DONATION AND RISK OF INFECTION
- P02.03 Anne Høy Seemann Vestergaard. END-OF-LIFE TRAJECTORIES OF CANCER VERSUS CHRONIC ILLNESSES: A NATIONWIDE STUDY
- P02.04 Camilla Cederbek Kjeldsen. REAL TIME URGE REGISTRATION WITH A SMARTPHONE APP AMONG PATIENTS WITH FECAL INCONTINENCE
- P02.05 Anne-Sofie Greve Christensen. THE EFFECT OF P2-RECEPTOR INHIBITION ON THE CYTOTOXIC EFFECT OF ALFA-HAEMOLYSIN FROM E.COLI - A MURINE SEPSIS MODEL
- P02.06 Sissel Ravn. THE INCIDENCE AND MORBIDITY OF INCISIONAL HERNIAS AFTER CYTOREDUCTIVE SURGERY WITH HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY: AN OBSERVATIONAL PROSPECTIVE COHORT STUDY
- P02.07 Katrine Overgaard Andersen. GASTROINTESTINAL MOTILITY AND SLEEP DISTURBANCES IN QUIESCENT CROHN'S DISEASE
- P02.08 Kasper Grooss. CANCER DIAGNOSIS AND CHANGE OF GENERAL PRACTITIONER
- P02.09 Søren Viborg. LOWER GASTROINTESTINAL BLEEDING AND RISK OF GASTROINTESTINAL CANCER
- P02.10 Jens Tilma. TREATMENT INJURIES IN DANISH PUBLIC HOSPITALS 2006-2012

## Poster session 3

Chairmen: Lars Bolund & Mette Lausten Hansen (PhD student)

- P03.01 Carina Madsen. MATERNAL COFFEE CONSUMPTION DURING PREGNANCY AND RISK OF CHILDHOOD ACUTE LEUKEMIA
- P03.02 Sham Husain. MRI AND PET/CT SCAN USED IN STAGING OF CERVICAL CANCER BEFORE SURGERY
- P03.03 Anna Hartmann Schmidt. LOCAL RECURRENCE AND LATE COMPLICATIONS AFTER SIMPLE RESECTION OF RESIDUAL METASTASIS AFTER CHEMOTHERAPY IN NON-SEMINOMATOUS TESTICULAR CANCER
- P03.04 Anne Møller. PROSTANOID-INDUCED CONTRACTION OF HUMAN PLACENTAL STEM VILLI VEINS IS MODULATED BY A PERIVASCULAR-DERIVED DILATION FACTOR
- P03.05 Ulla Juul Christiansen. LAPAROSCOPIC HYSTERECTOMY - A RANDOMIZED CONTROLLED STUDY ON OUTPATIENT VERSUS INPATIENT REGIMEN

- P03.06 Thor Haahr. DOES BACTERIAL VAGINOSIS AFFECT FEMALE FECUNDITY?
- P03.07 Saga Elise Mariansdatter. MATERNAL PRE-PREGNANCY BMI AND REPRODUCTIVE HEALTH OF DAUGHTERS IN YOUNG ADULthood
- P03.08 Lotte Kaasgaard Jakobsen. UROGENITAL RECONSTRUCTIVE SURGERY

## Poster session 4

Chairmen: Robert Fenton, Nikolaj Rittig (PhD student) & Zahra Nochi (PhD student)

- P04.01 Jonas Jensen. INFLUENCE OF ORGANIC CATION TRANSPORTER 1 AND 2 IN PHARMACOKINETIC OF METFORMIN
- P04.02 Dina Michelle Baarts Pedersen. THE ROLE OF MICRORNAs IN OBSTRUCTIVE NEPHROPATHY
- P04.03 Stine Høgsholt. HEALTH CONDITION IN SURVIVORS OF WILMS TUMOR: A NORDIC POPULATION-BASED COHORT STUDY
- P04.04 Jeppe Steen Olsen. SODIUM/BICARBONATE-COTRANSPORTER SLC4A7 MEDIATES THE INCREASED BASOLATERAL BICARBONATE UPTAKE IN RENAL THICK ASCENDING LIMBS DURING METABOLIC ACIDOSIS
- P04.05 Silje Jørgensen Hovden. EXPANDING THE SPECTRUM OF GENETIC VARIATION CAUSING FAMILIAL HYPOCALCIURIC HYPERCALCEMIA AND AUTOSOMAL DOMINANT HYPOCALCEMIA
- P04.06 Samuel Levi Clement Svendsen. P2X RECEPTOR-MEDIATED INHIBITION OF NaCl ABSORPTION IN THE THICK ASCENDING LIMB: NO EVIDENCE FOR NO
- P04.07 Lea Lykke Braskhøj Lauridsen. PUBERTAL DEVELOPMENT AND SEMEN QUALITY AND REPRODUCTIVE HORMONES IN YOUNG ADULT LIFE
- P04.08 Rahul Prabha. ENGINEERED BONE FOR OSSEOUS RESTORATION
- P04.09 Marie Bodilsen. RENAL BIOMARKERS AFTER DECEASED DONOR KIDNEY TRANSPLANTATION
- P04.10 Lise Sofie Bislev. PHYSIOLOGIC INTERACTIONS BETWEEN THE ADRENAL AND THE PARATHYROID GLANDS DESCRIBED BY CONTROLLED CLINICAL TRIALS - A DESCRIPTION OF A PHD PROJECT

## Poster session 5

Chairmen: Natalya Fedosova, Randi Heidemann Gottfredsen (PhD student) & Anna Budtz-Lilly (PhD student)

- P05.01 Kris Chadwick Hede. BONE MARROW ASPIRATE FOR CARTILAGE REPAIR
- P05.02 Iben Jensen. THE NATRIURETIC RESPONSE TO ACUTE POTASSIUM INTAKE
- P05.03 Henrik Jonathan Münch. THE ASSOCIATION BETWEEN METAL ALLERGY, TOTAL KNEE ARTHROPLASTY AND REVISION

- P05.04 Hang Nguyen Nielsen. CONSEQUENCES OF MUTATION TO GLN923 FOR NA<sup>+</sup> AND K<sup>+</sup> BINDING IN NA<sup>+</sup>/K<sup>+</sup>-ATPASE
- P05.05 Signe Kierkegaard. THE HAFAI-COHORT: OUTCOME AFTER ARTHROSCOPIC TREATMENT OF PATIENTS IN HORSSENS AND AARHUS WITH FEMORAL ACETABULAR IMPINGEMENT, DESIGN OF A PROSPECTIVE COHORT STUDY
- P05.06 Stine Mikkelsen. STABILITY CLUSTER LINKS HYDROPHOBIC GATE TO K873 IN ATP8A2
- P05.07 Mia Børsmose Trip. VALIDATION OF BIOMARKERS ASSOCIATED WITH METASTASIS IN BLADDER CANCER
- P05.08 Søren Skaarup. SAFETY AND QUALITY OF ULTRASOUND-GUIDED INTRALYMPHATIC ALLERGEN SPECIFIC IMMUNOTHERAPY
- P05.09 Lene Maria Ørts. THE VALUE AND FINDINGS OF EARLY SPIROMETRY IN TWO DIFFERENT SETTINGS
- P05.10 Eva Boysen. BLOOD SAMPLE MONITORING OF EGFR M+ LUNG CANCER

## Poster session 6

Chairmen: Mai Marie Holm & Veerle Paternoster (PhD student)

- P06.01 Thorsten Kamlarczyk Rasmussen. PROCEDURE-RELATED REDUCED AUTONOMIC RESPONSE DURING THE VALSALVA MANOEUVRE
- P06.02 Mads Qvist Ebbesen. THE PROGNOSTIC VALUE OF QUANTITATIVE ELECTROENCEPHALOGRAPHY IN COMATOSE NEUROSURGICAL PATIENTS
- P06.03 Ellen Lund Schaldemose. NO ASSOCIATION OF POLYMORPHISMS IN THE SEROTONIN TRANSPORTER GENE WITH THERMAL PAIN SENSATION IN HEALTHY INDIVIDUALS
- P06.04 Trine Ellegaard. PATIENT CONTROLLED ADMISSIONS IN PSYCHIATRY- A NATIONAL EXPLORATIVE STUDY OF 'USER-CONTROLLED BEDS'
- P06.05 Anne Sofie Vinther. INSULIN-LIKE GROWTH FACTORS IN THE CEREBROSPINAL FLUID FROM PATIENTS WITH DEMENTIA
- P06.06 Alexander Juhl Andersen. POST MASTECTOMY PAIN SYNDROME - CLASSIFICATION, PREVALENCE AND RISK FACTORS
- P06.07 Kathrine Dyhr Lycke. IMPACT OF PSYCHIATRIC DISORDERS ON INTENSIVE CARE ADMISSION, QUALITY OF CARE, AND MORTALITY AFTER COLORECTAL CANCER SURGERY
- P06.08 Kirstine Krushave Lehm. NON-URGENT 112-CALLERS - WHO ARE THEY, AND WHAT HAPPENS TO THEM?

## Poster session 7

Chairmen: Johan Palmfeldt & Kristian Krogh (PhD student)

- P07.01 Laura Sommer Hansen. HEART FAILURE IS THE LEADING CAUSE OF DEATH THE YEAR AFTER CARDIAC SURGERY REGARDLESS OF PREOPERATIVE HEART FUNCTION

- P07.02 Jeppe Bakkestrøm Rosenbæk. THE EFFECT OF SODIUM NITRITE ON BLOOD PRESSURE, GLOMERULAR FILTRATION RATE AND FRACTIONAL SODIUM EXCRETION IN HEALTHY SUBJECTS
- P07.03 Astrid Drivsholm Sloth. ECONOMIC EVALUATION OF REMOTE ISCHAEMIC CONDITIONING AS AN ADJUNCT TO PRIMARY PERCUTANEOUS CORONARY INTERVENTION IN PATIENTS WITH ST-ELEVATION MYOCARDIAL INFARCTION: A STUDY PROTOCOL
- P07.04 Adrian Bauer. FOURTEEN YEARS OF MINIMAL INVASIVE EXTRACORPOREAL CIRCULATION (MIECC) AND STILL OPEN QUESTIONS?!
- P07.05 Bodil Gade Hornstrup. NOCTURNAL BLOOD PRESSURE IN CHRONIC KIDNEY DISEASE, HYPERTENSION AND OBSTRUCTIVE SLEEP APNEA - CENTRAL AND PERIPHERAL 24-HOUR BLOOD PRESSURE MEASUREMENTS
- P07.06 Dmitrii Kamaev. CELLULAR FUNCTION OF THE  $Ca^{2+}$ -ACTIVATED  $Cl^-$  CHANNEL PROTEIN - TMEM16A - IN THE ARTERIAL WALL. THE STUDY FROM KNOCKOUT MICE
- P07.07 Tinne Tranberg. MECHANICAL CHEST COMPRESSIONS IMPROVE QUALITY OF CPR IN OUT-OF-HOSPITAL CARDIAC ARREST
- P07.08 Willemijn Comuth. ADHERENCE AND THE ROLE OF COAGULATION ASSAYS IN PATIENTS TREATED WITH DABIGATRAN ETEXILATE FOR NON-VALVULAR ATRIAL FIBRILLATION (ARCADE STUDY)

## Poster session 8

Chairmen: Torsten Bloch Rasmussen & Anne Dorte Blankholm (PhD student)

- P08.01 Jens Sundbøll. PREADMISSION USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS OR ANGIOTENSIN RECEPTOR BLOCKERS AND SHORT-TERM MORTALITY AFTER STROKE: A NATIONWIDE POPULATION-BASED COHORT STUDY
- P08.02 Vibeke Lynggaard. LEARNING AND COPING STRATEGIES IMPROVES ADHERENCE IN CARDIAC REHABILITATION
- P08.03 Christina Mørup Jørgensen. OXYGEN SATURATION IN CENTRAL AND PERIPHERAL RETINAL VESSELS IN PATIENTS WITH TREATMENT REQUIRING DIABETIC RETINOPATHY
- P08.04 Johan Frederik Berg Arendt. ELEVATED PLASMA VITAMIN B12 AND RISK OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH CANCER
- P08.05 Christoffer Tobias Witt. ADHERENCE TO EVIDENCE-BASED PHARMACOTHERAPY IN PATIENTS WITH SYSTOLIC HEART FAILURE AND CARDIAC RESYNCHRONIZATION THERAPY DURING LONG-TERM FOLLOW-UP
- P08.06 Kasper Pryds. REMOTE ISCHEMIC CONDITIONING ATTENUATES THE EFFECT OF HEALTH-CARE SYSTEM DELAY IN STEMI PATIENTS TREATED WITH PRIMARY PERCUTANEOUS CORONARY INTERVENTION
- P08.07 Line Pedersen. THE REGULATION OF RETINAL ARTERIOLES DURING HYPOXIA ARE MODIFIED BY NO AND COX PRODUCTS
- P08.08 Peter Rubak. CYCLOOXYGENASE-1 AND 2 IN PLATELETS: IS THERE AN ASSOCIATION

WITH IMMATURE PLATELET FRACTION AND PLATELET FUNCTION

P08.09 Morten Krogh Christiansen. PREMATURE CORONARY ARTERY DISEASE - CLINICAL AND MOLECULAR GENETIC ASPECTS

P08.10 Junjing Su. WAVE INTENSITY ANALYSIS IN THE PULMONARY ARTERY

## Poster session 9

Chairmen: Elise Røge Hedegaard & Helene Tilma Vistisen (PhD student)

P09.01 Rikke Elmose Mols. VISUALIZATION OF CORONARY ARTERY CALCIFICATION AND THE INFLUENCE ON PREVENTIVE THERAPY AND LIFESTYLE MODIFICATION

P09.02 Anni Jeppesen. DOES HYPOTHERMIA AFTER CARDIAC ARREST INFLUENCE HEMOSTASIS?

P09.03 Mia Benedicte Lykke Roest Laursen. CELL MODEL FOR METABOLOMICS STUDIES OF REMOTE ISCHEMIC CONDITIONING

P09.04 Jeong Shim. APOE-KNOCKOUT AND ATHEROSCLEROSIS IN MINIPIGS

P09.05 Kristian Løkke Funck. ARTERIAL STIFFNESS AND COMPLICATION RISK IN TYPE 2 DIABETES

P09.06 Nils Henrik Hansson. AORTIC VALVE STENOSIS AND LEFT VENTRICULAR EFFICIENCY

P09.07 Tor Skibsted Clemmensen. ASSESSMENT OF VASCULOPATHY USING CORONARY FLOW VELOCITY RESERVE AND 2D-SPECKLE TRACKING ECHOCARDIOGRAPHY DURING SEMI SUPINE EXERCISE TEST

P09.08 Sarah Holmboe. DIFFERENTIAL EFFECTS OF PROSTACYCLIN ANALOGUES ON RIGHT VENTRICULAR FUNCTION IN THE ISOLATED RAT HEART

## Poster session 10

Chairmen: Donna Briggs Bødtkjær & Christian Bo Poulsen (PhD student)

P10.01 Wieke Haakma. VISUALIZING THE VESSELS IN POST MORTEM BODIES USING COMPUTED TOMOGRAPHY ANGIOGRAPHY

P10.02 Michala Herskind Sejr. DETECTION OF ATRIAL FIBRILLATION IN STROKE AND TCI PATIENTS

P10.03 Morten Thingemann Bøtker. DYSPNEA - A LETHAL SYMPTOM IN PATIENTS PRESENTING TO THE PREHOSPITAL EMERGENCY MEDICAL SERVICE

P10.04 Anders Krogh Brøndberg. ABORTED SCD IN THE YOUNG CAUSED BY NON-ISCHEMIC INHERITED HEART DISEASE - CLINICAL AND NEW MOLECULAR-GENETIC ASPECTS

P10.05 Christian Reuss Mikkelsen. DO DRUGS CAUSE SUDDEN DEATH AMONG PSYCHIATRIC PATIENTS? - A STUDY ON POLYPHARMACY AND ARRHYTHMIA

P10.06 Sara Gaur. FRACTIONAL FLOW RESERVE DERIVED FROM CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY: VARIATION OF REPEATED ANALYSES

- P10.07 Lisbeth Bonde. PERIVASCULAR TISSUE AFFECTS REGULATION OF CORONARY ARTERY TONE
- P10.08 Trine Ørhøj. BIORESORBABLE STENTS FOR TREATMENT OF CORONARY BIFURCATION LESIONS ASSESSED BY OPTICAL COHERENCE TOMOGRAPHY
- P10.09 Anders Grejs. CARDIAC EFFECTS OF PROLONGED HYPOTHERMIA AFTER CARDIAC ARREST
- P10.10 Peter Skov Jensen. A NEW MODEL FOR STUDYING DIAMETER REGULATION OF PORCINE RETINAL ARTERIOLES AND CAPILLARIES IN VITRO

## Poster session 11

Chairmen: Torbjørn Brøgger (PhD student)

- P11.01 Maria Rasmussen. ANOMALIES OF THE KIDNEYS DIAGNOSED BY PRENATAL ULTRASOUND SCREENING AND ASSOCIATED NONURINARY BIRTH DEFECTS: A NATIONWIDE PREVALENCE STUDY
- P11.02 Anders Møllekær. THE ORGANIZATION OF DANISH EMERGENCY DEPARTMENTS
- P11.03 Mads Riiskjær. EARLY RISE IN SERUM C-REACTIVE PROTEIN INDICATES SUBSEQUENT SURGICAL COMPLICATION AFTER LOW ANTERIOR RESECTION FOR RECTO-SIGMOID ENDOMETRIOSIS
- P11.04 Mia Steengaard Olesen. THERAPEUTIC ENDOMETRIAL TRAUMA FOR ENHANCEMENT OF EMBRYO IMPLANTATION
- P11.05 Gitte Øskov Skajaa. INSULIN SENSITIVITY DURING PREGNANCY AND POST PARTUM
- P11.06 Lise Hald Nielsen. ATTENUATED SENSITIVITY OF ALDOSTERONE IN RESPONSE TO DIETARY SALT IN PREECLAMPSIA IS COMPATIBLE WITH ABERRANT ACTIVATION OF ENAC
- P11.07 Anne Gisselmann Egekvist. CONSERVATIVE TREATMENT OF RECTOSIGMOID ENDOMETRIOSIS MONITORED BY TRANSVAGINAL ULTRASOUND
- P11.08 Martin Christensen. PREECLAMPSIA AND ARTERIAL STIFFNESS - A 10-YEAR FOLLOW-UP OF PREVIOUSLY PREECLAMPTIC WOMEN
- P11.09 Lise Haaber Thomsen. THE USE OF PREIMPLANTATION FACTOR (PIF) IN OPTIMIZING EMBRYO SELECTION IN IVF TREATMENT - A DESCRIPTIVE COHORT STUDY IN FOUR DANISH IVF CLINICS
- P11.10 Rune Dall Jensen. DREAM TEAM - A PREGRADUATE SURGICAL TALENT DEVELOPMENT PROJECT

## Poster session 12

Chairmen: Jens Leipziger & Sara Heebøll (PhD student)

- P12.01 Susanne Haas. ALTERED CORTICAL PROCESSING IN RESPONSE TO RECTAL AND ANAL STIMULI IN PATIENTS SUFFERING FROM IDIOPATHIC FECAL INCONTINENCE
- P12.02 Anders Mark Christensen. ROBOT-ASSISTED ILEOANAL ANASTOMOSIS - COMPARISON



#### OF EARLY OUTCOME WITH CONVENTIONAL LAPAROSCOPY

- P12.03 Michelle Meier. THE PROTEOMIC RESPONSE TO LIVER INJURY AND REGENERATION - AN EXPERIMENTAL RAT STUDY
- P12.04 Kirstine Petrea Bak-Fredslund. MANAGEMENT OF PATIENTS WITH HEPATOCELLULAR CARCINOMA: CLINICAL IMPACT OF  $^{18}\text{F}$ -FDGGAL PET/CT MOLECULAR IMAGING WITH LABELLED GALACTOSE TRACER  $^{18}\text{F}$ FDGAL
- P12.05 Casper Larsen. STRUCTURAL AND FUNCTIONAL STUDIES OF COBALAMIN UPTAKE AND TRANSPORT
- P12.06 Linda Skibsted Kornerup. MILK IS AN EXCELLENT SOURCE FOR VITAMIN B12. AN EXPERIMENTAL STUDY IN A RAT MODEL
- P12.07 Emilie Glavind. ALCOHOLIC HEPATITIS MARKEDLY DECREASES THE CAPACITY FOR UREA SYNTHESIS
- P12.08 Nikolaj Worm Ørntoft. HEPATIC TRANSPORT OF CONJUGATED BILE ACIDS IN HUMANS QUANTIFIED BY  $^{11}\text{C}$ -CHOLYLSARCOSINE PET/CT
- P12.09 Anne Grosen. INFLUENCE OF AZATHIOPRINE TREATMENT ON SEMEN QUALITY IN MEN WITH INFLAMMATORY BOWEL DISEASE
- P12.10 Lea Ladegaard Grønkjær. ORAL HEALTH STATUS OF PATIENTS WITH LIVER CIRRHOSIS

### Poster session 13

Chairmen: Marianne Uhre Jakobsen & Maria Charlotte Steffensen (PhD student)

- P13.01 Sigrid Bjerger Gribsholt. NON-SURGICAL COMPLICATIONS AND CHANGES IN QUALITY OF LIFE AFTER GASTRIC BYPASS SURGERY
- P13.02 Max Norman Tandrup Lambert. THE EFFECTS AND MECHANISMS OF BIOAVAILABLE RED CLOVER ISOFLAVONES ON MENOPAUSAL SYMPTOMS AND BONE RESORPTION
- P13.03 Sofie Hertz Rønn. TREATMENT WITH VITAMIN K2: A RANDOMIZED CONTROLLED CLINICAL TRIAL, INVESTIGATING THE EFFECT ON BONE METABOLISM, INSULIN SENSITIVITY AND ARTERIAL STIFFNESS
- P13.04 Ann Bjørnshave. DOSE-RESPONSE EFFECT OF WHEY PROTEIN CONSUMED AS PRE-MEAL ON POSTPRANDIAL LIPEMIA IN PERSONS WITH THE METABOLIC SYNDROME
- P13.05 Morten Højild Pedersen. SUBSTRATE METABOLISM, GROWTH HORMONE (GH) SIGNALING, AND INSULIN SENSITIVITY DURING FASTING IN LEAN AND OBESE HUMAN SUBJECTS AND THE IMPACT OF GROWTH HORMONE RECEPTOR (GHR) BLOCKADE
- P13.06 Peter Breining. EFFECTS OF HYPERTHYROIDISM ON AMOUNT AND ACTIVITY OF BROWN ADIPOSE TISSUE
- P13.07 Tanni Kjær Borgbo. SIZE MATTERS: THE EFFECTS OF THE ANDROGEN RECEPTOR CAG REPEAT LENGTH ON HUMAN ANTRAL FOLLICLE FUNCTION
- P13.08 Lise Bols Andersen. CHARACTERIZATION OF THE CLINICAL AND MOLECULAR EFFECTS OF A NOVEL AVP SIGNAL PEPTIDE MUTATION

## Poster session 14

Chairmen: Peter Bross, Navid Sahebekhtari (PhD student) & Anne Kristine Amstrup (PhD student)

- P14.01 Mark Klitgaard Nøhr. RESVERATROL AMELIORATES LIPOPOLYSACCHARIDE-INDUCED INSULIN RESISTANCE IN MICE
- P14.02 Mads Vandsted Svart. THE ROLE OF ATGL AND G0/G1 SWITCH GENE COMPLEX IN LPS INDUCED KETOACIDOSIS
- P14.03 Jesper Løkke Mehlsen. EFFECT OF PROTEIN HIGH IN LEUCINE ON MUSCLE PROTEIN BALANCE IN FRAIL ELDERLY PATIENTS. ACUTE STUDY WITH PROTEIN-TRACER-TECHNIQUES
- P14.04 Thomas Schmidt Voss. METABOLIC SIGNALING IN HUMAN MUSCLE AND ADIPOSE TISSUE FOLLOWING HYPOGLYCEMIA
- P14.05 Sascha Pilemann-Lyberg. URIC ACID ASSOCIATED WITH DECLINE OF GFR IN DIABETIC NEPHROPATHY
- P14.06 Agnethe Berglund. THE EPIDEMIOLOGY OF GROWTH HORMONE DEFICIENCY; A NATIONWIDE COHORT STUDY
- P14.07 Joan Bach Nielsen. CONTINUOUS GLUCOSE MONITORING FOR EVALUATION OF HYPOGLYCEMIA AFTER ROUX-EN-Y GASTRIC BYPASS
- P14.08 Pia Deichgræber. THE MACROPHAGE MARKER SOLUBLE CD163 AND ITS ASSOCIATION WITH NEPHROPATHY AMONG INDIVIDUALS WITH SCREEN DETECTED TYPE 2 DIABETES

## Poster session 15

Chairmen: Niels H. Birkebæk, Christian Bjerregaard Olesen (PhD student) & Christian Lottrup (PhD student)

- P15.01 Anil Anil. RISK OF INFECTIONS AMONG TYPE 2 DIABETES PATIENTS: AN 18-YEAR NATIONWIDE COHORT STUDY
- P15.02 Anne Grethe Schioldan. EFFECTS OF A DIET RICH IN ARABINOXYLAN AND RESISTANT STARCH VERSUS A LOW-FIBRE DIET ON LIPID AND CARBOHYDRATE METABOLISM IN SUBJECTS WITH METABOLIC SYNDROME
- P15.03 Anne Sofie Korsholm Nielsen. OBSTRUCTIVE SLEEP APNEA AND THE EFFECT OF CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP), WEIGHT LOSS AND THE BIOACTIVE COMPOUND RESVERATROL ON INFLAMMATION
- P15.04 Pedram Shokouh. EFFECTS OF NATURAL AND ENRICHED UNFILTERED COFFEE ON LIVER FAT CONTENT AND GLUCOSE AND LIPID METABOLISM IN NON-ALCOHOLIC FATTY LIVER DISEASE - AN IN-VIVO EVALUATION USING HYPERPOLARIZED MRI BIOPROBES
- P15.05 Michael Væggemose. MR DIAGNOSTICS OF DIABETIC PERIPHERAL NEUROPATHY

- P15.06 Elias Sundelin. PHARMACOKINETIC IMAGING OF METFORMIN USING [<sup>11</sup>C]METFORMIN
- P15.07 Henrik Holm Thomsen. REFUTING ENDOTOXIN TOLERANCE IN HUMANS
- P15.08 Rikke Hjortebjerg. IGFBP-4 FRAGMENT LEVELS ARE UNAFFECTED IN PATIENTS WITH ST-ELEVATION MYOCARDIAL INFARCTION TREATED WITH HEPARIN AND PCI

## Poster session 16

Chairmen: Irene Dige & Maj Høygård Nicolaisen (PhD student)

- P16.01 Shun-Ichi Suzuki. BLOOD OXYGENATION OF THE MASSETER MUSCLE DURING SUSTAINED ELEVATED MUSCLE ACTIVITY
- P16.02 Line Staun. FLUORIDE IN DENTAL BIOFILM AND SALIVA
- P16.03 Mats Bue. PHARMACOKINETICS OF VANCOMYCIN IN PORCINE BONE OBTAINED BY MICRODIALYSIS
- P16.04 Simple Futarmal Kothari. SOMATOSENSORY ASSESSMENT AND CONDITIONED PAIN MODULATION IN TEMPOROMANDIBULAR DISORDERS PAIN PATIENTS
- P16.05 Kristian Friesgaard Christensen. EFFECTIVENESS AND SAFETY OF INTRAVENOUS FENTANYL ADMINISTERED BY AMBULANCE PERSONNEL
- P16.06 Bahram Ranjkesh. IS SELF-REPAIR IN GAPS POSSIBLE? STUDY OF APATITE PRECIPITATION IN THE GAPS BETWEEN THE NEW DENTAL MATERIAL (IMTA) AND DENTIN
- P16.07 Kristian Andersen. EFFECT OF UNILATERAL MANDIBULAR DISTRACTION OSTEOGENESIS ON MANDIBULAR MORPHOLOGY IN RABBITS WITH ANTIGEN-INDUCED TMJ ARTHRITIS
- P16.08 Natasja Leth Jørgensen. HUMAN CHONDROCYTES CULTURED ON MODIFIED POLYSTYRENE CONSERVE THEIR CHONDROGENIC PHENOTYPE IN VITRO

## Poster session 17

Chairmen: Efe Levent Aras & Sepp de Raedt (PhD student)

- P17.01 Pia Kjær Kristensen. HIGHER HIP FRACTURE UNIT VOLUME ASSOCIATED WITH POORER QUALITY OF IN-HOSPITAL CARE, LONGER LENGTH OF STAY AND INCREASED 30-DAY MORTALITY
- P17.02 Thomas Dahl Nielsen. DURATION OF ANALGESIA AFTER FEMORAL NERVE BLOCK WITH BUPIVACAINE AND DEXAMETHASONE IN PATIENTS WITH FEMORAL NECK FRACTURE
- P17.03 Bjørn Borsøe Christensen. LIMITED OSTEOCHONDRAL REPAIR BY A BIOMIMETIC COLLAGEN SCAFFOLD - ONE TO THREE YEARS CLINICAL AND RADIOLOGICAL FOLLOW-UP
- P17.04 Daan Koppens. PROMISING RESULTS OF THE SIGMA UNICOMPARTMENTAL KNEE ARTHROPLASTY, 1-YEAR FOLLOW-UP WITH RSA
- P17.05 Rehne Lessmann Hansen. EVALUATION OF PERI-IMPLANT BONE MINERAL DENSITY CHANGES AFTER FEMORAL OSSEOINTEGRATED PROSTHESIS SURGERY

- P17.06 Morten Lykke Olesen. CARTIGEN PRO® FOR CARTILAGE REPAIR
- P17.07 Lone Dragnes Brix. UNSCHEDULED CONTACTS WITH HEALTH SERVICES AFTER OUTPATIENT KNEE ARTHROSCOPY: PRELIMINARY RESULTS FROM AN OBSERVATIONAL FOLLOW-UP STUDY
- P17.08 Ahmed Abdul-Hussein Abood. A NOVEL TREATMENT TECHNIQUE WITH STEM CELLS (MSC) AND MINCED CARTILAGE FOR THE PREVENTION OF PHYSEAL BONE BRIDGE FORMATION IN A STANDARDIZED EXPERIMENTAL PORCINE MODEL
- P17.09 Eva Natalia Glassou. LONG TERM ASSOCIATION BETWEEN HOSPITAL PROCEDURE VOLUME AND REVISION AFTER TOTAL HIP ARTHROPLASTY: A STUDY WITHIN THE NORDIC ARTHROPLASTY REGISTER ASSOCIATION DATABASE
- P17.10 Steffan Tábori Jensen. HIGHER UHMWPE WEAR RATE IN CEMENTLESS COMPARED WITH CEMENTED CUPS WITH THE SATURNE® DUAL-MOBILITY SYSTEM

## Poster session 18

Chairmen: Casper Foldager & Mette Winther (PhD student)

- P18.01 Janne Brammer Damsgaard. THE ILLNESS TRAJECTORY OF SPINE FUSION PATIENTS. A FEELING OF BEING (IN)VISIBLE
- P18.02 Mette Holland-Fischer. RHEUMATOID ARTHRITIS AND MORTALITY FOLLOWING HOSPITALIZED PNEUMONIA; A POPULATION-BASED COHORT STUDY WITH DIAGNOSIS VALIDATION
- P18.03 Yongfu Yu. MORTALITY TRENDS AND LEVELS IN CHILDREN AGED 0-9 YEARS: A NATIONWIDE COHORT STUDY FROM THREE NORDIC COUNTRIES
- P18.04 Janni Lisander Larsen. THE LURKING OF THE WOLF-QUALITATIVE RESEARCH OF EXISTENTIAL EXPERIENCES IN FEMALE PATIENTS SUFFERING FROM LUPUS
- P18.05 Nini Nørgaard. UNDERSTANDING METHOTREXATE INDUCED GASTROINTESTINAL TOXICITY IN JUVENILE IDIOPATHIC ARTHRITIS
- P18.06 Daniel Ramskov Jørgensen. THE DESIGN OF THE RUN CLEVER RANDOMIZED CONTROLLED TRIAL: THE FOCUS OF A RUNNING SCHEDULE AND ITS ASSOCIATION WITH THE RISK OF RUNNING RELATED INJURIES
- P18.07 Rasmus Cleemann. DOSAGES-RESPONSE OF BONE MORPHOGENIC PROTEIN ON A BACKGROUND OF SYSTEMIC BISPHOSPHONATE IN AN UNLOADED CANINE IMPLANT MODEL

## Poster session 19

Chairmen: Yonglun Luo & Aida Solhøj Hansen (PhD student)

- P19.01 Line Kibsgaard. MASTOCYTOSIS AND THE RISK OF ANAPHYLAXIS
- P19.02 Alexander Fjældstad. OLFACTORY SCREENING: VALIDATION OF SNIFFIN' STICKS IN DENMARK
- P19.03 Sandra Kruchov Thygesen. RESPIRATORY DISTRESS SYNDROME IN MODERATELY

PRETERM INFANTS AND RISK OF EPILEPSY: A POPULATION-BASED STUDY

- P19.04 Troels Johansen. MAPPING LOCAL OXYGEN AND CO<sub>2</sub> TRANSFER RATES IN THE LUNG
- P19.05 Kristine Zøylner Rubeck. INTRA- AND INTER-OBSERVATORY VARIATION OF THYROID SHEAR WAVE ELASTOGRAPHY - A VARIABILITY STUDY
- P19.06 Christian F. P. Scholz. GENOME-WIDE ANALYSIS REVEALS OPTIMAL SINGLE LOCUS TYPING SCHEME FOR P. ACNES
- P19.07 Mette Nygaard Christensen. TRACHEOMALACIA DIAGNOSED BY MULTIDETECTOR COMPUTED TOMOGRAPHY: AN EVALUATION OF DIFFERENT IMAGE ANALYSIS
- P19.08 Nina Viskum Hogaard. ASTMAVEN - INCREASED VENTILATION IN HOMES OF ASTHMATIC CHILDREN: AN INTERVENTION STUDY
- P19.09 Mette Sørensen Langfrits. SHARED CARE AND IMPLEMENTATION OF A PEDIATRIC ASTHMA CLINICAL PATHWAY
- P19.10 Camilla Askov Mousing. PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) WISH TO DISCUSS PALLIATIVE CARE WITH HEALTH PROFESSIONALS

## Poster session 20

Chairmen: Morten Nielsen & Sofie Christiansen (PhD student)

- P20.01 Lene Duez. ADDED VALUE OF MAGNETOENCEPHALOGRAPHY IN THE DANISH PRESURGICAL EPILEPSY EVALUATION
- P20.02 Mikkel Petersen. USING MRI BASED TRACTOGRAPHY TO DETERMINE SUBTHALAMIC NUCLEUS CONNECTIVITY IN PARKINSON'S PATIENTS UNDERGOING DEEP BRAIN STIMULATION
- P20.03 Kousik Sarathy Sridharan. STUDYING SOMATOSENSORY FUNCTION IN PARKINSON'S DISEASE
- P20.04 Thorbjørn Søndergaard Engedal. THE ROLE OF MICROVASCULAR DYSFUNCTION IN ISCHEMIC STROKE
- P20.05 Anna Szyszka. DNA METHYLATION OF CACNA1C IN BIPOLAR DISORDER
- P20.06 Mette Kragh. WAKE AND LIGHT THERAPY TO INPATIENTS WITH MAJOR DEPRESSION - EFFICACY, PREDICTORS AND PATIENT EXPERIENCES
- P20.07 Rikke Hahn Kofoed. INVESTIGATING A PLK-2 DEPENDENT ALPHA-SYNUCLEIN CATABOLIC PATHWAY
- P20.08 Marianne von Euler Chelplin. NEUROPROTECTIVE ROLE OF REGULATORY T CELLS IN PARKINSONS DISEASE: EFFECT OF COP-1/ALPHA-SYNUCLEIN VACCINATION ON PATHOLOGY PROGRESSION

## Poster session 21

Chairmen: Carmela Matrone & Gro Helen Dale (PhD student)

- P21.01 Noemie Regine Virginie Tentillier. ANTI-INFLAMMATORY THERAPY VIA CD163-

## MACROPHAGES IN THE 6-OHDA PARKINSON'S DISEASE MODEL

- P21.02 Erhard Næss-Schmidt. MICROSTRUCTURAL CHANGES IN THE BRAIN AFTER CONCUSSION
- P21.03 Peter Parbo. THE RELATIONSHIP BETWEEN BETA-AMYLOID, TAU AND BRAIN INFLAMMATION IN SUBJECTS AT RISK OF DEVELOPING ALZHEIMER'S DISEASE. A PET STUDY
- P21.04 Hugo Angleys. THE EFFECTS OF CAPILLARY TRANSIT TIME HETEROGENEITY (CTH) ON BRAIN OXYGENATION
- P21.05 Kira Vibe Jespersen. MUSIC FOR INSOMNIA - A COCHRANE REVIEW AND META-ANALYSIS
- P21.06 Esben Ahlburg Eickhardt. ENRICHMENT ANALYSIS OF GENOMIC FEATURES TO IDENTIFY GENOME-WIDE PATTERNS OF INSERTIONS/DELETIONS IN CASES OF PSYCHIATRIC DISORDERS FROM THE FAROE ISLANDS
- P21.07 Maria Hørhold Christensen. INNATE IMMUNE EVASION BY THE HERPES SIMPLEX VIRUS - 1 PROTEIN ICP27
- P21.08 H.C. Nørgaard. METABOLIC PROFILES OF 429 PATIENTS WITH SCHIZOPHRENIA AND INCREASED WAIST CIRCUMFERENCE: BASELINE DATA FROM THE CHANGE TRIAL
- P21.09 Alyssa Huebner. DEVELOPING PLURIPOTENT STEM CELLS AS MODELS FOR STUDYING PARKINSON'S DISEASE IN VITRO
- P21.10 Zongpei Zhao. STRUCTURE OF A NEURONAL PROTEIN COMPLEX INVOLVED IN NEURODEGENERATIVE DISEASE

## Poster session 22

Chairmen: Jens R Nyengaard & Maryam Ardalan (PhD student)

- P22.01 Amanda Eskelund. ALTERED TRYPTOPHAN METABOLISM IN A GENETIC RAT MODEL OF DEPRESSION
- P22.02 Mads Engel Hauberg. DISSECTING THE ROLE OF MICRORNAS IN THE ETIOLOGY OF SCHIZOPHRENIA
- P22.03 Kristian Lundsgaard Kraglund. PLATELETS & SEROTONIN
- P22.04 Martin Brandhøj Skov. EXTRACELLULAR  $Mg^{2+}$  AND  $Ca^{2+}$  REDUCE MYOTONIA IN CLC-1 INHIBITED ISOLATED HUMAN MUSCLE
- P22.05 Arnela Mehmedbasic. SORLA'S INFLUENCE ON RETINAL APP PROCESSING
- P22.06 Anders Abildgaard. PROBIOTIC TREATMENT HAS ANTI-DEPRESSANT EFFECT INDEPENDENT OF DIET
- P22.07 Ali Khalidan Vibholm. PRECLINICAL IN-VIVO IMAGING OF ACTIVATED NMDA RECEPTOR ION CHANNELS WITH THE NOVEL RADIOLIGAND  $^{18}F$ -GE179
- P22.08 Inga Christensen. ATYPICALLY LOCATED PROTEINS IN A NORMALLY POLARIZED EPITHELIUM

P22.09 Anders Gunnarsson. STEM CELLS IN THE EPIDERMIS: INVESTIGATING THE RELATION BETWEEN GENE EXPRESSION, EPIGENETIC MARKS AND CELL POSITIONING

## Poster session 23

Chairmen: Simon Fristed Eskildsen & Abhishek Kumar (PhD student)

- P23.01 Le Le STRUCTURAL STUDIES OF PROTEIN COMPLEXES BY MOLECULAR ELECTRON MICROSCOPY
- P23.02 Toke Jost Isaksen. UNDERSTANDING THE PATHOLOGY OF ALTERNATING HEMIPLEGIA OF CHILDHOOD USING KNOCK-IN MICE
- P23.03 Iben Rahbek Andersen. DYNAMIC CONTRAST-ENHANCED CT IN THE FOLLOW-UP OF IMAGE-GUIDED LIVER INTERVENTIONS
- P23.04 Gudrun Winther. MATERNAL PERINATAL HIGH-FAT DIET INCREASES ANXIETY-LIKE BEHAVIOR IN OFFSPRING
- P23.05 Maj Ulrichsen. SORTILINS IN PERIPHERAL NERVE REGENERATION
- P23.06 Arndis Simonsen. IMPLICIT AND EXPLICIT SOCIAL INFLUENCE ON DECISION-MAKING IN SCHIZOPHRENIA
- P23.07 Michael Aagaard Andersen. LOSS OF LEUCINE-RICH-REPEAT-KINASE-2 REVERSES INCREASED IRREGULARITY FIRING IN SUBTHALAMIC NUCLEUS INDUCED BY VIRAL OVEREXPRESSION OF  $\alpha$ -SYNUCLEIN IN VIVO
- P23.08 Sakthidasan Jayaprakash. TOWARDS CHARACTERIZING A MACROMOLECULAR COMPLEX INVOLVED IN CONTROLLING NEURONAL DIFFERENTIATION
- P23.09 Ali H. Rafati. SPATIAL DISTRIBUTION OF NEURONS IN LAYER-III OF MEDIAL PREFRONTAL CORTEX OF FLINDERS RATS WITH MATERNAL SEPARATION
- P23.10 Hong Sain Ooi. A FRAMEWORK TO EVALUATE THE QUALITY OF PROTEIN INTERACTION NETWORK

## Poster session 24

Chairmen: Erik Johnsen & Anette Riisgaard Ribe (PhD student)

- P24.01 Esben Nielsen. FUCHS ENDOTHELIAL DYSTROPHY: CLINICAL CHARACTERISTICS, TREATMENT OUTCOME, AND PATHOLOGY
- P24.02 Christophe Henri Valdemar Duez. EARLY NEUROLOGICAL PROGNOSTICATION WITH BIOMARKERS OF PATIENTS IN THERAPEUTIC HYPOTHERMIA AFTER CARDIAC ARREST
- P24.03 Sven Robert Andresen. THE EFFECT OF NORMAST (PEA) IN NEUROPATHIC PAIN IN SPINAL CORD INJURY
- P24.04 Andreas Nørgaard Glud. LARGE ANIMAL PARKINSONS DISEASE MODELS USING VIRAL VECTORS AND INOCULATION OF PREFORMED FIBRILS TO MEDIATE ALPHA-SYNUCLEIN OVEREXPRESSION AND MISFOLDING IN THE GOTTINGEN MINIPIG CNS
- P24.05 Rebeka Bodak. AUDITORY EXPOSURE AND THE ENHANCEMENT OF NEW MOTOR MEMORIES

- P24.06 Krystian Figlewski. TRANSCRANIAL DIRECT CURRENT STIMULATION COMBINED WITH TREADMILL TRAINING IN THE SUBACUTE PHASE FOLLOWING STROKE: CASE SERIES
- P24.07 Maryam Anzabi. INFLUENCE OF PERICAPILLARY NITRIC OXIDE LEVELS AND EDEMA ON CAPILLARY BLOOD FLOW PATTERNS IN MOUSE MODELS OF SUBARACHNOID HEMORRHAGE
- P24.08 Trine Gjerløff. THE NOVEL PET TRACER <sup>11</sup>C-DONEPEZIL DEMONSTRATES DECREASED PARASYMPATHETIC INNERVATION IN THE GUT AND PANCREAS OF PATIENTS WITH PARKINSON'S DISEASE
- P24.09 Omar Majed Abuyaman. THE SOLUBLE RECEPTOR FOR VITAMIN B12 UPTAKE (SCD320) IS PRESENT IN CEREBROSPINAL FLUID AND CORRELATES TO THE DEMENTIA MARKERS TAU PROTEINS AND AMYLOID BETA
- P24.10 Lena-Sophie Martis. COGNITIVE PHENOTYPING OF A RAT CMS DEPRESSION MODEL USING TOUCHSCREEN OPERANT PLATFORM

## Poster session 25

Chairmen: Mads V. Sørensen, Lu Xing (PhD student) & Louise Bill (PhD student)

- P25.01 Brigitta Villumsen. THE IMPACT OF EXERCISE IN MEN WITH PROSTATE CANCER RECEIVING ANDROGEN DEPRIVATION THERAPY
- P25.02 Lise Høj Thomsen. IDENTIFICATION OF TGF- $\beta$  DEPENDENT/INDEPENDENT PATHWAYS IN ANIMAL MODELS OF EARLY-STAGE DIABETIC NEPHROPATHY
- P25.03 Hanne Mari Jørgensen. N-3 POLYUNSATURATED FATTY ACIDS AND BONE DENSITY IN RENAL TRANSPLANT RECIPIENTS
- P25.04 Pernille Skjold Kingo. C-REACTIVE PROTEIN CONCENTRATION - COMPARISON BETWEEN ROBOT ASSISTED LAPAROSCOPIC CYSTECTOMY AND OPEN MINI-LAPAROTOMY CYSTECTOMY
- P25.05 Tommy Kjærgaard Nielsen. LAPAROSCOPIC CRYOABLATION OF SMALL RENAL TUMORS - DOES ANATOMICAL TUMOR COMPLEXITY EFFECT TREATMENT OUTCOME?
- P25.06 Steven Brantlov. BIOIMPEDANCE ANALYSIS IN CHILDREN AGED 0-14 YEARS: IS THERE A RELATION BETWEEN PHASE ANGLE, WEIGHT AND BODY SURFACE AREA?
- P25.07 Maria Elkjær. MULTI-PARAMETRIC MAGNETIC RESONANCE IMAGING IN THE DIAGNOSIS AND SURVEILANCE OF PROSTATE CANCER
- P25.08 Danny Jensen. THE ESSENTIAL ROLE OF PROXIMAL TUBULE ENDOCYTIC RECEPTORS FOR THE URINARY EXCRETION OF ENDOGENOUS CYSTATIN C
- P25.09 Casper Kierulf Lassen. THE ROLE OF REMOTE ISCHEMIC CONDITIONING IN RENAL ISCHEMIA-REPERFUSION INJURY
- P25.10 Michael Christensen. RENOPROTECTIVE EFFECTS OF METFORMIN IN RESPONSE TO UNILATERAL URETERAL OBSTRUCTION IN MICE



## Poster session 26

Chairmen: Morten Ladekarl & Anne Vestergaard (PhD student)

- P26.01 Anne Wandler. MICRORNA EXPRESSION DIFFERS BETWEEN MELANOCYTIC NEVI AND MELANOMA - A MICROARRAY ANALYSIS
- P26.02 Chaitali Laura Ollars. BEREAVEMENT SUPPORT IN PALLIATIVE CARE - A RANDOMISED CONTROLLED TRIAL (RCT)
- P26.03 Marianne Hjorth Skorstengaard. ADVANCE CARE PLANNING IN DENMARK
- P26.04 Kennet Sønderstgaard Thorup. INTRAVOXEL INCOHERENT MOTION (IVIM) ANALYSIS OF DIFFUSION WEIGHTED MAGNETIC RESONANCE IMAGING (DWI) ALLOWS ESTIMATION OF DIFFUSION AND PERFUSION DIFFUSION RELATED PARAMETERS
- P26.05 Kim Sivesgaard. WHOLE BODY MRI COULD AID IN THE DETECTION OF EXTRA-HEPATIC COLORECTAL CANCER METASTASES
- P26.06 Anne Kruse Hollensen. ENHANCED MICRORNA SUPPRESSION ACTIVITY OF RNA POL II-TRANSCRIBED TOUGH DECOY INHIBITORS FUSED TO WPRE
- P26.07 Ninna Cathrine Schmidt Voss. REGULATION OF ACID-BASE BALANCE AND BLOOD PERFUSION IN HUMAN COLON CANCER
- P26.08 Morten Nørgaard Andersen. LIPOSOME-BASED SPECIFIC TARGETING OF DRUGS TO CANCER-PROMOTING MACROPHAGES: A NOVEL THERAPUTIC PARADIGM IN MULTIPLE MYELOMA

## Poster session 27

Chairmen: Tine Engberg Damsgaard, Jakob Kristian Jakobsen (PhD student) & Maja Ølholm Vase (PhD student)

- P27.01 Birgitte Sandfeld Paulsen. ULTRA-MICRO SAMPLES CAN BE USED FOR MRNA ANALYSIS FOR LUNG CANCER RELEVANT BIOMARKERS
- P27.02 Kristian Løvvik Juul-Dam. EARLY DETECTION OF RELAPSE OF ACUTE MYELOID LEUKEMIA IN CHILDREN
- P27.03 Trine Majken Gade Bonnesen. LIVER DISEASES IN ADULT LIFE AFTER CHILDHOOD CANCER IN SCANDINAVIA (ALICCS): A POPULATION-BASED COHORT STUDY
- P27.04 Jakob Toftegaard. MOVING METAL ARTIFACT REDUCTION IN CONE-BEAM CT SCANS WITH IMPLANTED CYLINDRICAL GOLD MARKERS
- P27.05 Mette Skovgaard Christensen. EXPOSURE TO STYRENE AND RISK OF CANCER: A LONG-TERM FOLLOW-UP STUDY OF WORKERS IN THE DANISH REINFORCED PLASTICS INDUSTRY
- P27.06 Oscar Casares Magaz. SPATIAL DOSE RESPONSE RELATIONS FOR RECTAL MORBIDITY FOLLOWING HIGH-PRECISION RADIOTHERAPY
- P27.07 Mia Møller. INCREASED SENSITIVITY OF PROSTATE CANCER DIAGNOSIS BASED ON MULTIGENE MODELS OF DNA METHYLATION AS CANCER FIELD EFFECTS

- P27.08 Ane Bundsbæk Iversen. DO METFORMIN AND OTHER BIGUANIDES HAVE A ROLE IN ANTICANCER TREATMENT?
- P27.09 Heidi Buvarp Dyrop. TUMOR CHARACTERISTICS, PATIENT REPORTED SYMPTOMS AND SUSPECTED AND FINAL DIAGNOSIS FOR 64 SARCOMA PATIENTS REFERRED TO A SARCOMA CENTER AFTER SURGERY/BIOPSY IN NON-SPECIALIST INSTITUTIONS
- P27.10 Mai-Britt Bjørklund Ellegaard. PATIENT-LEAD FOLLOW-UP AFTER ADJUVANT THERAPY FOR BREAST CANCER IN AN ONCOLOGICAL DEPARTMENT

## Poster session 28

Chairmen: Michael R. Horsman & Søren Haack (PhD student)

- P28.01 Johanne Bach Andersen. SERIAL MONITORING OF CIRCULATING MICRORNAS IN ERLOTINIB TREATED LUNG CANCER PATIENTS
- P28.02 Line M Hybel Schack. PREDICTION OF RADIATION INDUCED TOXICITY - PROJECT DESCRIPTION
- P28.03 Katrine Rye Hauerslev. BREAST CANCER: SHOULDER DISABILITY AND LATE SYMPTOMS FOLLOWING ONCOPLASTIC BREAST SURGERY
- P28.04 Marie Toft-Petersen. HIGH FRACTIONS OF CD34+CD38- CELLS WITH ABERRANT HMICL EXPRESSION PREDICT SHORTER OVERALL AND PROGRESSION FREE SURVIVAL IN MYELODYSPLASTIC SYNDROME
- P28.05 Susanne Rylander. A DIFFERENTIAL DOSE PRESCRIPTION STRATEGY IN PERMANENT LOW-DOSE-RATE PROSTATE BRACHYTHERAPY
- P28.06 Mathilde Thomsen. CHARACTERIZATION OF TUMOR HETEROGENEITY AND CELLULAR SUBPOPULATIONS IN BLADDER CANCER PATIENTS WITH PROGRESSIVE DISEASE
- P28.07 Peter Asdahl. ESOPHAGEAL STRICTURES AMONG CHILDHOOD CANCER SURVIVORS: A REPORT FROM THE ADULT LIFE AFTER CHILDHOOD CANCER IN SCANDINAVIA (ALICCS) STUDY
- P28.08 Anne Winther Larsen. EGFR CA REPEAT POLYMORPHISM PREDICTS CLINICAL OUTCOME IN EGFR MUTATION POSITIVE NSCLC PATIENTS TREATED WITH ERLOTINIB

## Poster session 29

Chairmen: Klaus Krogh, Michał Świtnicki (PhD student) & Jill Rachel Mains (PhD student)

- P29.01 Mette Heisz Ørndrup. MELANOMA IN SITU: A SINGLE-CENTRE EXPERIENCE WITH 479 PATIENTS
- P29.02 Ditte Løhmann. TOXICITY IS ASSOCIATED WITH AGE IN NOPHO-AML 2004
- P29.03 Christina Demuth. FIBROBLASTS STIMULATE LUNG-CANCER CELL GROWTH AND INFLUENCE THE RESPONSE TO EGFR TARGETED TREATMENT
- P29.04 Anna Kirstine Winthereik. GENERAL PRACTITIONERS' WILLINGNESS TO PAY HOME VISITS AND THE LIKELIHOOD OF THEIR PATIENTS TO STAY OUT OF HOSPITAL AND DIE AT HOME - A NATIONWIDE DANISH REGISTER-BASED COHORT STUDY

- P29.05 Mai Lykkegaard Schmidt. CLINICAL USE OF ITERATIVE 4D CBCT RECONSTRUCTIONS TO INVESTIGATE LUNG TUMOR MOTION
- P29.06 Lone Vedel Schøler. TUMOR SPECIFIC GENOMIC VARIATIONS, A BASIS FOR PERSONALIZED CRC MANAGEMENT
- P29.07 Ditte Louise Egeskov Munkedal. POST-OPERATIVE MULTI-DISCIPLINARY TEAM MEETINGS HAVE A POSITIVE EFFECT ON THE SURGICAL QUALITY IN COLON CANCER
- P29.08 Ellen Marie Høye. A NEW DOSIMETER FORMULATION FOR DEFORMABLE 3D DOSE VERIFICATION
- P29.09 Jenny Bertholet. TARGET TRANSLATION, ROTATION AND DEFORMATION DURING LIVER STEREOTACTIC BODY RADIATION THERAPY
- P29.10 Sigrid Salling Árnadóttir. DEVELOPMENT OF A NOVEL ASSAY FOR MONITORING COLORECTAL CANCER BY DETECTION OF KRAS AND BRAF MUTATIONS IN CIRCULATING TUMOR DNA

## Poster session 30

Chairmen: Niels Gregersen & Lea Hougaard Pedersen (PhD student)

- P30.01 Rikke Madsen. PATIENT AND RELATIVE EXPERIENCES CONCERNING TRANSITIONS FROM A COURSE OF INCURABLE CANCER
- P30.02 Yuduo Zheng. TOXICITY OF SILVER NANO-PARTICLES AND ULTRAFINE COMBUSTION PARTICLES ON A549 CELLS
- P30.03 Sara Francis. IDENTIFICATION OF THE SPOUSE'S RESPONSIBILITIES, FUNCTIONS AND ROLES IN RELATION TO CARE FOR A LOVED ONE WITH A PRIMARY BRAIN TUMOUR
- P30.04 Jesper Beck Jørgensen. MESORECTAL EXCISION FOR RECTAL CANCER: ASPECTS OF RECURRENCE AND SURVIVAL
- P30.05 Steffen Filskov Sørensen. DYNAMICS OF CIRCULATING TUMOR DNA IN PATIENTS WITH NON-SMALL CELL LUNG CANCER
- P30.06 Anne Ramlov. RELATIONSHIP BETWEEN LYMPH NODE DOSE AND NODAL OUTCOME IN LOCALLY ADVANCED CERVICAL CANCER
- P30.07 Line Brøndum. PLASMA MARKERS IN HEAD AND NECK CANCER IN CORRELATION TO FAZA PET CT AND A HYPOXIC GENE PROFILE

## Poster session 31

Chairmen: Uffe Birk Jensen & Moslem Ranjbar (PhD student)

- P31.01 Anna Sundby. WHOLE GENOME SEQUENCING - NEW POSSIBILITIES, NEW DILEMMAS
- P31.02 Monica Milter Ehlers. A SYSTEMATIC REVIEW OF QUALITATIVE AND QUANTITATIVE STUDIES 2001 – 2014

- P31.03 Jakob Søgaard Juul. THE USE OF IMMUNOCHEMICAL FAECAL OCCULT BLOOD TEST (IFOBT) IN GENERAL PRACTICE. A STUDY OF PARTICIPANTS IN SCREENING, THE IMPLEMENTATION OF IFOB IN GENERAL PRACTICE AND THE RISK OF COLORECTAL CANCER IN CASE OF NEGATIVE IFOB
- P31.04 Marie Tvillum Petersen. THE CLINICAL IMPLICATION OF INTRODUCING ADAPTIVE RADIOTHERAPY IN THE TREATMENT OF LUNG CANCER PATIENTS
- P31.05 Peter Sinkjær Kenney. NASAL FILTERS APPEAR USEFUL IN PREVENTING SEASONAL ALLERGIC RHINITIS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CROSSOVER CLINICAL TRIAL
- P31.06 Louise Stride Nielsen. CHEMICAL FINGERPRINTING OF ILLEGAL DRUGS
- P31.07 Yan Zhou. REPROGRAMMING OF MCADD PATIENT FIBROBLAST INTO INDUCED PLURIPOTENT STEM CELLS USING A LENTIVIRUS-BASED GENE DELIVERY
- P31.08 Rasha Abdelkadhém Al-Saaidi. GENOME ENGINEERING OF THE CARDIOMYOCYTES-SPECIFIC MYOSIN HEAVY CHAIN GENE (MYH6) USING THE RNA- GUIDED CRISPR/CAS-9 SYSTEM TO FOLLOW CARDIAC DIFFERENTIATION

## Poster session 32

Chairmen: Marianne Lisby & Camilla Hoffmann Merrild (PhD student)

- P32.01 Laura Ozer Kettner. PARENTAL SUBFERTILITY AND EPILEPSY IN THE CHILD: A STUDY FROM THE AARHUS BIRTH COHORT
- P32.02 Jette Lauritzen. THE MEANINGFULNESS OF PARTICIPATING IN SUPPORT GROUPS FOR INFORMAL CAREGIVERS OF OLDER ADULTS WITH DEMENTIA: A QUALITATIVE SYSTEMATIC REVIEW
- P32.03 Christine Ladegaard Geyti. SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS ASSOCIATED TO POOR MENTAL HEALTH IN 30-49 YEAR-OLDS
- P32.04 Marianne Eg. MAPPING THE NATIONAL TREATMENT FOR OBESE CHILDREN AND ADOLESCENTS IN DENMARK. A QUESTIONNAIRE STUDY OF 19 DANISH PAEDIATRIC WARDS
- P32.05 Linn Berger Håkonsen. GENITAL MALFORMATIONS IN BOYS IN RELATION TO GESTATIONAL RISK FACTORS AND FETAL GROWTH RESTRICTION
- P32.06 Susanne Hvolgaard Mikkelsen. MATERNAL PRE-PREGNANCY BMI AND ADHD SYMPTOMS IN THE OFFSPRING
- P32.07 Signe Timm. PLACE OF UPBRINGING IN EARLY CHILDHOOD AS RELATED TO INFLAMMATORY BOWEL DISEASES IN ADULTHOOD - A POPULATION-BASED COHORT STUDY IN NORTHERN EUROPE
- P32.08 Ingrid Nilsson. PARENTS' EXPERIENCES OF EARLY POSTNATAL DISCHARGE
- P32.09 Susan Larsen. UNPLANNED ADMISSION IN HAEMATOLOGY: A QUANTITATIVE AND QUALITATIVE STUDY ON EXTENT, CAUSE AND IMPACT ON PATIENT'S LIFE
- P32.10 David Rurik Martinsson. CHILD AND ADOLESCENT OCD SYMPTOM PATTERNS: A FACTOR ANALYTIC STUDY

## Poster session 33

Chairmen: Simon Tilma Vistisen & Cathrine Carlsen Bach (PhD student)

- P33.01 Stine Daugaard Pedersen. INDOOR WORK, ULTRAVIOLET RADIATION, LIGHT EXPOSURE, AND THE RISK OF DEPRESSION AND MULTIPLE SCLEROSIS
- P33.02 Sorosh Tabatabaeifar. CARPAL TUNNEL SYNDROME AND CARPAL TUNNEL SYNDROME-LIKE SYMPTOMS IN RELATION TO MECHANICAL EXPOSURES ASSESSED BY A JOB EXPOSURE MATRIX: A TRIPLE CASE-REFERENT STUDY
- P33.03 Giovanni Ometto. NUMBER AND LOCATION OF LESIONS FOR THE OPTIMISATION OF THE SCREENING INTERVAL IN DIABETIC RETINOPATHY
- P33.04 Claus Hedebo Bisgaard. ACCELERATED LEARNING IN ANESTHESIOLOGY
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- P34.02 Birthe Annamarie Thomsen. NON-ATTENDANCE IN SCREENING FOR CARDIO-VASCULAR DISEASES (CVD) AND DIABETES (DM) AMONG DANISH WOMEN
- P34.03 Marie Mortensen. CONSTRUCT VALIDITY OF THE PERCEIVED STRESS SCALE AMONG ADULT DANES IN THE CENTRAL DENMARK REGION
- P34.04 Mette Lise Lousdal. COUNTY-BASED TRENDS IN BREAST CANCER STAGE DISTRIBUTION IN RELATION TO ORGANIZED SCREENING IN NORWAY: AN OPEN COHORT STUDY
- P34.05 Sanne Marie Thyssen. CHILDHOOD VACCINATIONS AND CHILD SURVIVAL IN GUINEA-BISSAU: A REANALYSIS
- P34.06 Tina Wang Vedelø. OPTIMISATION OF THE INTEGRATED BRAIN CANCER PATHWAY; A STUDY OF PATIENT EXPERIENCES AND NEED FOR INFORMATION, CARE AND SUPPORT
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- P34.09 Nikolaj Raaber. EMERGENCY MEDICAL TECHNICIAN TREAT-AND-LEAVE PATIENTS RECEIVING TELEMEDICINE CONSULTATION WITH EMERGENCY MEDICAL DISPATCH PHYSICIAN - A CONTROLLED BEFORE AND AFTER PILOT STUDY
- P34.10 Lene Odgaard Hellmund. ACCESS TO HIGHLY SPECIALIZED REHABILITATION FOLLOWING SEVERE TRAUMATIC BRAIN INJURY

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- P35.01 Annette Zøylner. PATIENT INVOLVEMENT IN DEVELOPMENT OF DIFFERENTIATED CLINICAL PATHWAY PROGRAMMES IN WOMEN WITH BREAST CANCER
- P35.02 Anne Sofie Dam Laursen. AN EPIDEMIOLOGICAL INVESTIGATION OF DAIRY PRODUCT INTAKE AND SUBSEQUENT RISK OF STROKE
- P35.03 Tove Lise Nielsen. HOME-BASED REHABILITATION FOR COMMUNITY DWELLING ELDERLY CITIZENS - A STUDY OF EFFECT AND CITIZENS' PERSPECTIVES
- P35.04 Sofie Ilsvard. GENERAL PRACTITIONERS' DISCRETIONS IN PREVENTIVE CONTEXTS - A QUALITATIVE INTERVIEW STUDY OF HOW GENERAL PRACTITIONERS' LIFESTYLE SPILLS OVER TO THEIR PREVENTIVE STRATEGIES
- P35.05 Maria Wielsøe. BREAST CANCER RISK IN THE GREENLANDIC INUIT POPULATION
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- P35.07 Line Hvidberg. BARRIERS TO HEALTHCARE SEEKING, BELIEFS ABOUT CANCER AND THE ROLE OF SOCIO-ECONOMIC POSITION. A DANISH POPULATION-BASED STUDY
- P35.08 Jörg Schullehner. DRINKING WATER N-POLLUTION AND PUBLIC HEALTH EFFECTS: NITRATE EXPOSURE OF THE DANISH POPULATION DURING THE LAST 35 YEARS

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- P36.03 Liv Solvår Nymark. ECONOMIC EVALUATION OF ALTERNATIVE MEASLES-MUMPS-RUBELLA VACCINATION SCHEDULES IN DANISH CHILDREN
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(CME) ON GENERAL PRACTITIONERS' KNOWLEDGE AND ATTITUDE

- P36.06 Anne Mette Falstie-Jensen. FULL COMPLIANCE WITH HOSPITAL ACCREDITATION WAS ASSOCIATED WITH LOWER 30-DAY MORTALITY RISK
- P36.07 Susanne Friis Søndergård. DOCUMENTATIONS OF NURSING ACTIVITIES AND PATIENT SAFETY IN THE OPERATION ROOM - THE SIGNIFICANCE OF A STUDY VISIT
- P36.08 Lotte Maxild Mortensen. N-3 AND N-6 PUFAS; INTERACTIONS, GENETIC PATHWAYS AND RISK OF ATRIAL FIBRILLATION

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- P37.02 Flemming Kromann Nielsen. MEASUREMENT OF BONE MARROW LESIONS BY MR IMAGING IN KNEE OSTEOARTHRITIS: THE SENSITIVITY TO CHANGE ASSESSED BY TWO QUANTITATIVE METHODS
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- P37.04 Kristina Margareta Öbrink-Hansen. MOXIFLOXACIN PHARMACOKINETIC PROFILE AND EFFICACY EVALUATION IN THE EMPIRIC TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA
- P37.05 Kasper Lisager Jønsson. HISTONE DEACETYLASE INHIBITORS PROTECTS CD4+T-CELLS FROM HIV-1 INFECTION
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- P37.08 Sofie Eg Jørgensen. MDA5 MUTATION IMPAIRS INFLAMMATORY AND ANTIVIRAL RESPONSES IN A PATIENT WITH ECTODERMAL DYSPLASIA WITH IMMUNODEFICIENCY

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- P38.01 Jesper Weile. INITIAL PATIENT EVALUATION IN THE EMERGENCY DEPARTMENT WITH POINT-OF-CARE ULTRASONOGRAPHY
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- P38.03 Lars Skov Dalgaard. RISK AND PROGNOSIS OF BACTERAEMIA AMONG PATIENTS ON CHRONIC PERITONEAL DIALYSIS: A POPULATION-BASED COHORT STUDY
- P38.04 Claus Sixtus Jensen. EARLY WARNING SYSTEM ON EVOLVING CRITICAL ILLNESS AND INTERVENTION IN HOSPITALISED CHILDREN; A REGIONAL MULTICENTRE STUDY ON

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## Abstracts

Tue  
Wenzel  
Kragstrup

### IL-20 AND IL-24 LINK RHEUMATOID FACTOR POSITIVITY AND BONE DESTRUCTION VIA THE IL-22R SUBUNIT IN RHEUMATOID ARTHRITIS

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Rheumatoid arthritis (RA) is an autoimmune disease characterized by the presence of inflammation and rheumatoid factor (RF) and destruction of the joints by osteoclasts (OC). The biologics (e.g. anti-TNF $\alpha$ ) have revolutionized modern rheumatology but still one third of patients treated with these drugs have insufficient responses. Thus, new candidates for modulatory treatment are needed. Recently, the receptor complexes IL-20R2/IL-20R1 and IL-20R2/IL-22R were identified as novel RA risk loci. These receptors are utilized by IL-19, IL-20, and IL-24. Here, we clarify the potential of modulating this system in the treatment of RA.

We measured IL-19, IL-20 and IL-24 in plasma from early RA patients (n=152) and healthy controls (HC) (n=88). The concentrations of IL-20 and IL-24 were increased in RA patients compared with HC (P=0.0002 and P=0.0016, respectively) and in RF positive compared with RF negative RA patients (both P<0.0001). The RA patients with high plasma IL-20 and IL-24 showed radiographic progression after 12 months (both P<0.01) and after 24 months (both P<0.01). We used peripheral blood mononuclear cells (PBMC) and synovial fluid mononuclear cells (SFMC) from chronic RA patients and HC PBMC for in vitro experiments. The production of all three cytokines was increased after stimulation with immune complexes simulating the presence of RF. The IL-22R was expressed by OC precursors in RA SFMCs and in multinucleated OC and IL-20 and IL-24 activated these cells.

Together our data suggest that attenuation of the shared IL-22R subunit might have a beneficial effect on radiographic progression in especially RF positive RA.

Henry  
Jensen

### DIAGNOSTIC INTERVALS AND TUMOUR STAGE BEFORE AND AFTER IMPLEMENTATION OF STANDARDISED CANCER PATIENT PATHWAYS

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Background: Standardised cancer patient pathways (CPPs) have been introduced in many countries. Nevertheless, studies are sparse on the impact of CPP implementation on both tumour stage at diagnosis and diagnostic interval (DI), i.e. the time from the patient's first presentation of symptoms until the time of diagnosis.

Aim: To compare the DI after CPP implementation (2010) with the DI before (2004/2005) and during (2007/2008) CPP implementation in Denmark and likewise for the tumour stage at diagnosis.

Materials and methods: Data from GPs and registries was used in an ecological study to compare three cohorts of incident cancer patients listed with a GP before, during and after CPP implementation. We compared the DI using quantile regression and estimated the odds-ratio (OR) of being diagnosed with a local tumour stage using logistic regression.

Results: The DI was significantly shorter after CPP implementation at all investigated percentiles for all patients combined. The median DI was 17 (95%CI: 15;19) days shorter after CPP implementation than before; CCP-referred patients had significantly shorter DI than non-CPP referred patients. Preliminary analyses show that patients tend to be less likely to be diagnosed with a local tumour (OR=0.88 (95%CI:0.75;1.03)) after CPP implementation, especially for CPP-referred patients.

Conclusion: The DI was shorter after CPP implementation than before; CPP-referred patients had the shortest DI. This may indicate that CPPs benefit only patients referred to CPP. The tendency of lower likelihood of being diagnosed with local tumours needs further analyses.

Perspectives: Further studies are needed of the survival rates of different referral routes.

Konstantin  
Kazankov

THE MACROPHAGE ACTIVATION MARKER SOLUBLE CD163 IS A  
BIOMARKER OF LIVER DISEASE SEVERITY

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**Background:** Macrophages play an important role in non-alcoholic fatty liver disease (NAFLD) and contribute in the transition to steatohepatitis (NASH) and fibrosis. We hypothesized that soluble (s)CD163, a specific macrophage activation marker, would be elevated in association with NAFLD severity and serve as a predictor of disease activity and fibrosis.

**Methods:** sCD163 associations with biochemical and histological measures of hepatic inflammation and fibrosis were investigated in two independent cohorts of 171 and 174 NAFLD patients. Demographic, clinical, biochemical, and metabolic data were recorded at the time of liver biopsy; sCD163 was measured by ELISA.

**Results:** sCD163 increased in parallel with the severity of liver injury assessed by the NAFLD Activity Score (NAS) and the Kleiner fibrosis score in both the estimation and the validation cohort. Multivariate regression analyses demonstrated independent associations with the NAS and the fibrosis score in both cohorts. A sCD163-based NASH score (CD163-NASH) predicted severe necroinflammation ( $NAS \geq 5$ ) (Estimation: AUROC 0.82 (95% CI: 0.74-0.90), Validation: 0.75 (95% CI: 0.66-0.84)). Similarly, a sCD163-based fibrosis score (CD163-NAFLD-FS) was a robust predictor of advanced fibrosis ( $F \geq 3$ ) in both cohorts (Estimation: AUROC 0.85 (95% CI: 0.78-0.92), Validation: 0.83 (95% CI: 0.75-0.90)).

**Conclusion:** Soluble CD163 reflecting macrophage activation is independently associated with hepatic inflammation and fibrosis in NAFLD. Further, sCD163-based prediction models performed well in predicting  $NAS \geq 5$  and advanced fibrosis stage, suggesting that the scores represent a useful non-invasive marker of disease severity in NAFLD.

O01.01      Xiaoqin Liu      MATERNAL ANTIDEPRESSANTS USE DURING PREGNANCY AND ASTHMA IN THE OFFSPRING: A POPULATION-BASED COHORT STUDY

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**Objective:** Maternal depression during pregnancy might lead to asthma in the offspring, but the role of maternal medication in this association is not known. We aim to examine whether maternal antidepressants use during pregnancy can increase the risk of asthma in children.

**Methods:** We performed a cohort study among all live singletons born in

Denmark during 1996-2007. We identified mothers who had a diagnosis of depressive disorder and/or used antidepressants one year prior to or during the index pregnancy. We estimated the hazards ratio (HR) of asthma in children by maternal antidepressants use during pregnancy, using Cox proportional hazards regression model.

Results: Of 733,685 children identified, 84,683 children had diagnosis of asthma. A total of 21,371 children were exposed to prenatal maternal depression (i.e. a diagnosis of maternal depressive disorder or antidepressants use one year prior to or during pregnancy). Prenatal maternal depression was associated with 34% increased risk of asthma (95% confidence interval (CI): 1.29-1.39). Overall, 8,895 children were exposed to antidepressants in utero. In comparison to children of mothers with prenatal depression and no antidepressants use during pregnancy, the HR of asthma for any antidepressant use during pregnancy was 0.99 (95% CI: 0.92-1.07). The HRs for selective serotonin reuptake inhibitors, newer and older antidepressants use only were 0.94 (95% CI: 0.87-1.03), 1.11 (95% CI: 0.89-1.39), and 1.26 (95% CI: 1.02-1.56), respectively.

Conclusion: Maternal antidepressants use during pregnancy generally did not increase the risk of asthma. However, older antidepressant use was associated with an increased risk of asthma.

O01.02 Jette Pedersen DOES POST-DISCHARGE NUTRITIONAL SUPPORT TO MALNOURISHED GERIATRIC PATIENTS AFFECT ADL FUNCTION?

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Introduction: Low dietary intake in geriatric patients leads to loss of muscle mass, reduced activity of daily living (ADL), and loss of independence. Early discharge makes the continuity of nutritional support increasingly important in order to prevent deterioration and promote recovery.

Aim: To investigate if post-discharge nutritional support to malnourished geriatric patients affects ADL function.

Material and methods: Patients admitted to an acute geriatric ward, at risk of malnutrition, 75+ years, and living alone, were randomly allocated to nutritional support (home visitor or telephone calls) or to a control group. Exclusion criteria were terminal illness, cognitive impairment, or nursing home residence. The interventions included nutritional counseling and supplement at 1, 2, and 4 weeks after discharge. ADL (Barthel score) was measured at discharge and 8 weeks later. Data were analyzed by multivariate repeated measurements analysis.

Results: Barthel data were measured twice in 157 patients (home visit: 52, telephone: 51, and control: 54). Participants were comparable in relation to age, morbidity, and nutritional risk. Mean increase in Barthel score in the home visit group was 10.8 (95%CI: 7.8;13.8), 7.2 (95%CI: 2.8;11.6) in the telephone group, and 6.4 (95%CI: 1.7;11.1) in controls. The differences

were not statistically significant.

Conclusion: The results point at a positive influence of home visits by a dietician after discharge of malnourished patients from geriatric ward. However, as the difference between the groups is not significant, the study should be repeated in larger groups of patients.

O01.03      Charlotte  
                  Simony

HEART- SHAKING TRANSITIONS DURING CARDIAC REHABILITATION - A PHENOMENOLOGICAL-HERMENEUTIC STUDY OF PATIENTS' EXPERIENCES

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Background: To improve cardiac care and especially cardiac rehabilitation the patients' perspectives should be better addressed. Knowledge of the patients' experiences of cardiac problems when receiving the current standard treatment is therefore much needed. According to the National Danish Heart Plan for patients with unstable angina pectoris or non-ST-elevation myocardial infarction specialized out-patient cardiac rehabilitation during 1-2 months is offered after the acute treatment.

Aim: To investigate how patients with new onset coronary heart disease experience their life situation during the trajectory of cardiac rehabilitation.

Methods: Introductory field observations were made. Focus group interviews and individual interviews were conducted with 11 patients enrolled in the cardiac rehabilitation programme. A phenomenological hermeneutic interpretation was conducted, comprising three methodological steps: naïve reading, structural analysis and comprehensive interpretation.

Results: The overall concept was that the patients were Heart Shaken by a Demanding Journey in Cardiac Rehabilitation. Three themes emerged: Hard to accept the disease: patients found it demanding to initially face the disease; Understanding that life has become frail: patients understood that the disease was chronic and life-threatening; An altered Life: patients perceived comprehensive changes in their everyday life.

Conclusion: During the trajectory of cardiac rehabilitation, patients experience various challenging transitions leading to vulnerable integrity. Hence attention towards integrity is essential in order to support the patients through cardiac care.



- O01.04     Nanna Rolving Rasmussen     DOES A PREOPERATIVE COGNITIVE-BEHAVIOURAL INTERVENTION AFFECT DISABILITY, PAIN BEHAVIOUR, PAIN AND RETURN TO WORK THE FIRST YEAR AFTER LUMBAR SPINAL FUSION?
- N. Rolving<sup>1</sup>, C.V. Nielsen<sup>2</sup>, F.B. Christensen<sup>3</sup>, R. Holm<sup>4</sup>, C. Bünge<sup>3</sup>, L.G. Oestergaard<sup>1</sup>*
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- Background: Few published studies have looked at the potential of rehabilitation to improve outcomes following lumbar spinal fusion (LSF). Rehabilitation programmes using cognitive-behavioural therapy (CBT) are recommended. Further, initiating interventions preoperatively seems beneficial, but only limited data exists in the field of spine surgery.
- Aim: To examine the effect of a preoperative CBT for patients undergoing LSF.
- Methods: 90 patients with degenerative disease undergoing LSF were randomized to usual care (control group) or preoperative CBT and usual care (CBT group). Primary outcome was change in Oswestry Disability Index (ODI) from baseline to 1 year. Secondary outcomes were catastrophizing, fear-avoidance belief, work status and pain.
- Results: At 1-year follow-up there was no significant difference between the CBT group and the control group in ODI score ( $P = 0.053$ ). However, the CBT group had achieved a significant reduction of -15 points (-26;-4) already at 3 months (between group difference  $P=0.003$ ) and this reduction was maintained throughout the year. There were no differences between groups on any of the secondary outcomes.
- Conclusions: Participating in a preoperative CBT intervention in addition to usual care did not produce better outcomes after 1 year. Although the reduction in disability was achieved much faster in the CBT group, resulting in a significant difference between groups already three months after surgery, it did not translate into a faster return to work. Our findings support the need for further research into the use of targeted rehabilitation interventions among patients with elevated levels of catastrophizing and fear avoidance beliefs.
- O01.05     Mette Ladefoged     RETINAL VASCULAR INSULIN SIGNALING DIABETIC RETINOPATHY
- M. Ladefoged<sup>1,2</sup>, N. Junke<sup>2</sup>, C. Mayer<sup>2</sup>, T. Bek<sup>1</sup>*
- <sup>1</sup>Department of Ophthalmology, Aarhus University Hospital, <sup>2</sup>Department of Diabetes Complications Biology, Novo Nordisk A/S
- Background and objective: Diabetic retinopathy (DR) is damage to the retina caused by complications of diabetes resulting in a high risk of vision

loss. The pathogenesis of DR is multifactorial but is primarily caused by the metabolic effects of chronic hyperglycemia, resulting in retinal vascular changes and subsequent retinal injury. Laboratory and clinical data strongly suggest that altered insulin action, at least at the systemic level, might also play an important role in the pathogenesis of DR. However, there is limited knowledge about the actions of insulin in the retinal vasculature under normal and diabetic conditions. The purpose of this project is to study the expression and activity of the insulin receptor (IR) in retinal vessels, and to determine the effects of hyperglycemia on retinal insulin signaling.

Methods: Normoglycemic and hyperglycemic mice received either no treatment to study basal IR expression or an acute insulin infusion to activate the insulin signaling pathway. Eyes were enucleated, fixed and prepared for retinal whole mount and cross-sectional staining. Retinas were stained with either an anti-IR antibody or an anti-phospho-IR antibody, analyzed and quantified.

Results: Preliminary data indicate that the IR is expressed in the retinal vasculature of mice. The project is ongoing and further analysis will be performed within the next months.

Discussion: A better understanding of insulin signaling in DR will provide the opportunity to develop new drugs that enhance the general or specific actions of insulin and the insulin receptor in the retina.

O01.06 Ingeborg  
Hedegaard  
Kristensen

#### ARE HEALTH VISITORS' OBSERVATIONS OF EARLY PARENT-INFANT INTERACTIONS RELIABLE? A CROSS-SECTIONAL STUDY

*I.H. Kristensen*

Public Health

Introduction: Health visitors' assessment of the quality of parent-infant interaction is often critical to subsequent initiatives to promote early parent-infant relationship. Healthy relationship may lead to promote infants' psychosocial development. The objectives of this study are to explore health visitors' observation skills and their intention, self-efficacy, and knowledge relevant to promoting early parent-infant relationship.

Methods: This cross-sectional study included 121 Danish health visitors of whom 36 were Marte Meo therapists and 85 had no supplemental parenting program education. Their observation skills were measured in a test situation where they were asked to assess 5 video-recorded, mother-infant interactions master-coded with the Infant CARE-Index. A self-reported questionnaire was used to measure their intention, self-efficacy, and knowledge about early parent-infant relationship.

Results: Marte Meo therapists were significantly more skilled at assessing mother-infant interactions, and they had a significantly higher level of knowledge than health visitors without a parenting program education. The latter reported significantly higher need for further qualifications in parent-infant relations. No significant differences were seen between the

two groups with regard to intentions, self-efficacy, and working profile.

Conclusions: Although all health visitors have a high level of intention and self-efficacy, Marte Meo therapists were superior in terms of observation skills and knowledge. Further research is needed to determine whether the level of health visitors' knowledge and observation skills are associated with improved outcomes for parent-infant relationship.

- O02.01 Anne Cathrine S nderstgaard Thorup VINTAGE VEGETABLES IMPROVE THE HEALTH STATUS OF TYPE 2 DIABETICS WHEN COMPARED TO EQUIVALENT MODERN VEGETABLES

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Background: Vegetables are an important part of the human diet and a major source of biologically active substances called secondary metabolites. These secondary metabolites contribute to the nutritional quality of food giving it a bitter and strong taste, but more importantly are their potential health promoting effects.

Aim: To determine if a high dietary intake of bitter and strong tasting (BST) vegetables have a beneficial impact on insulin resistance related to type 2 diabetes (T2D) when compared to equivalent intake of modern mild and sweet (MST) tasting vegetables.

Method: The study was a 3-month randomized controlled parallel intervention study involving 86 participants aged 35-70 years with T2D. The participants were randomized into 3 different diets; 1) consuming daily 500 g of BST vegetables 2) 500 g daily of MST vegetables and 3) normal diet (control). Both vegetable diets (group 1 and 2) consisted of root vegetables and cabbages.

Results: Both diets high in vegetables did significantly reduce the participants BMI ( $p<0.0001$ ), fasting plasma glucose ( $p<0.05$ ), HbA1c ( $p<0.001$ ), fasting insulin concentration ( $p<0.05$ ) and HOMA-IR ( $p<0.05$ ). Furthermore, in the BST group significant differences were also found regarding average blood pressure from 24-h measurements ( $p<0.05$ ), body fat composition ( $p<0.01$ ), iAUC from OGTT (insulin ( $p<0.05$ ) and glucose ( $p<0.01$ )) and plasma lipids ( $p<0.05$ ).

Conclusion: The study shows that the vegetable diet with a high level of secondary metabolites, hence the bitter and strong taste, have higher health promoting effects when compared to an equivalent diet with modern mild and sweet tasting vegetables.

- O02.02 Casper Kornbech Larsen
- REDUCED RENAL K<sup>+</sup>EXCRETION WITH COMPENSATORY HYPER-ALDOSTERONISM IN K<sub>CA</sub>1.1 CHANNEL BETA<sub>2</sub>-SUBUNIT KO MICE
- C.K. Larsen, M. Sørensen, H.A. Prætorius, J. Leipziger*
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- The kidneys are the primary organs responsible for excreting K<sup>+</sup>, ensuring whole body K<sup>+</sup>homeostasis by precisely matching K<sup>+</sup> excretion to K<sup>+</sup> intake. K<sup>+</sup> is secreted into the urine in the collecting ducts, and two distinct mechanisms for K<sup>+</sup> secretion exist; a constitutive mechanism mediated by ROMK (Kir1.1) in principal cells and a flow-induced mechanism mediated by BK channels (K<sub>CA</sub>1.1) in intercalated cells. Both mechanisms are up-regulated by aldosterone. Here we studied renal K<sup>+</sup> excretion in KO mice for the β<sub>2</sub>-subunit of the BK channel.
- β<sub>2</sub>KO mice have increased plasma aldosterone, low renin expression and normal plasma [K<sup>+</sup>]. The low renin in β<sub>2</sub>KO mice indicates that a K<sup>+</sup> handling deficiency, rather than hypotension triggered hyperaldosteronism. We hypothesize that β<sub>2</sub>KO mice have decreased BK channel-mediated renal K<sup>+</sup> secretion, which is compensated by hyperaldosteronism and up-regulation of ROMK-mediated K<sup>+</sup> secretion, allowing β<sub>2</sub>KO mice to maintain normal plasma [K<sup>+</sup>]. In fact, when treated with eplerenone (mineralocorticoid receptor antagonist), β<sub>2</sub>KO mice develop slight hyperkalemia (4.15 mM ± 0.13 in WT vs. 4.60 mM ± 0.10 in KO, P = 0.013).
- Urinary K<sup>+</sup> excretion following oral K<sup>+</sup> load (20% of normal daily intake) was not different between WT and KO mice. However, when treated with eplerenone, β<sub>2</sub>KO mice had a significantly lower urinary K<sup>+</sup> excretion rate (P=0.044) and significantly higher plasma [K<sup>+</sup>] 3 hours after oral K<sup>+</sup> load (10.0 mM ± 0.4 in WT vs. 11.4 mM ± 0.5 in KO, P = 0.044). Our data support that hyperaldosteronism in β<sub>2</sub>KO mice is part of a chronic compensation to a decreased BK channel-mediated renal K<sup>+</sup> secretion.
- O02.03 Kirstine Kobberø Sogaard
- SPLANCHNIC VENOUS THROMBOSIS IS A MARKER OF CANCER AND A PROGNOSTIC FACTOR FOR CANCER SURVIVAL
- K.K. Sogaard*
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- Background: Splanchnic venous thrombosis (SVT) may be a marker for occult malignancy.
- Methods: Using Danish medical registries, we conducted a nationwide cohort study covering 1994-2011. We identified patients with a first-time SVT diagnosis and followed them for subsequent cancer diagnoses. We calculated absolute risk of cancer and the standardized incidence ratio, comparing risk observed in patients with SVT to that expected in the general population. We assessed the prognostic impact of SVT on cancer survival by applying the Kaplan-Meier methods and Cox regression, using

a comparison cohort of cancer patients without SVT (matched by gender, age, calendar year, and cancer type and stage).

Results: We identified 1,191 patients with SVT and followed them for a median of 1.6 years. The three-month cancer risk was 8.0% and the standardized incidence ratio was 33 (95% confidence interval [CI], 27 to 40). Increased risk was mainly found for liver cancer (risk=3.5%; standardized incidence ratio=1805 [95% CI, 1295 to 2448]), pancreatic cancer (risk=1.5%; standardized incidence ratio=256 [95% CI, 149 to 409]), and myeloproliferative neoplasms (risk=0.7%; standardized incidence ratio=764 [95% CI, 329 to 1505]). The overall standardized incidence ratio remained twofold increased after one or more years of follow-up, compared to the general population. SVT was a prognostic factor for liver and pancreatic cancer, but not for myeloproliferative neoplasms.

Conclusions: Splanchnic venous thrombosis is a marker of prevalent occult cancer and a prognostic factor for survival in patients with liver and pancreatic cancer.

O02.04 Jakob Dal

#### INCIDENCE AND LATE PROGNOSIS OF ACROMEGALY IN DENMARK: PRELIMINARY DATA

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Introduction: Acromegaly is a rare disease caused by GH hypersecretion from a pituitary adenoma. However, accurate estimates of incidence and prevalence are scarce and not based on nationwide populations. It is well known that surgical cure may normalize mortality and improve morbidity but similar data are not available for patients receiving medical treatment.

Method: We first validated the ICD-8 and -10 diagnosis codes for acromegaly in The National Registry of Patients by a systematic patient chart review of related diagnosis and pertinent clinical biochemistry. Data on the entire acromegaly cohort were then obtained by individual patient chart review and by using several national databases such as The Cancer Registry, The Registry of Cause of Death and The National Registry of Patients.

Results: The mean incidence rate of acromegaly from 1989 - 2010 was 3.8 cases /million/year (95% CI 3.6-4.1) with a prevalence of 85 cases/million in 2010. The mean age at diagnosis was 47 years (CI 95% 46-48) with a sex distribution on 49% males (CI 95% 45-53). We found a 1.4 (CI 95% 1.2-1.7) fold increased mortality among patients with acromegaly compared to the background population. The impact of different treatment modalities on mortality is under investigation.

Conclusion: This nationwide study is the first to provide accurate estimates of incidence and prevalence rates of acromegaly and to evaluate the impact of medical treatment as compared to surgery.

- O02.05 Marie Krarup  
Schrøder DURATION OF USE AND SAFETY OF DESMOPRESSIN IN BEDWETTING PATIENTS: RESULTS FROM 8 YEARS OF REGISTRATION OF 214,220 DESMOPRESSIN PRESCRIPTIONS TO 40,596 INDIVIDUAL USERS

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Desmopressin was approved for treating NE in 1982. Approximately 1 million prescriptions are written annually for NE, worldwide. Hyponatremia, associated with desmopressin, is considered rare in children (< 1/10.000 patients). We wished to provide an overview of the use of desmopressin in a nationwide cohort.

Through the National Prescription Registry we identified 40,596 pediatric bedwetting patients (< 18 years) and 214,220 desmopressin prescriptions. Sixty-six % were male. Mean age was 9.19 yrs ( $\pm 3$ ). Prescription data was linked to data from the National Patient Registry. Sixty-six % were prescribed melt, 18% tablets and 17% nasal-spray. Among melt-prescriptions, 26% were for 60  $\mu$ g, 66% 120  $\mu$ g and 8% 240 $\mu$ g. After titration 14 % of boys and 16 % boys were long term treated with 60 $\mu$ g. Treatment time increased with increasing doses (618 days for 240  $\mu$ g, 520 for 120  $\mu$ g and 394 for 60  $\mu$ g). Of the 240 $\mu$ g melt-users 8.4% had just 1 prescription. For lower melt doses, tablet and spray 22.9% to 52.1% were one-time users. None of the 40,596 pediatric desmopressin users were hospitalized with hyponatremia during the 8-year period.

The majority of NE patients were treated with melt. Surprisingly, 26% of the melt users were prescribed 60  $\mu$ g, which is intended for nocturia in adults. Even after correction for the titration period, which indicates that a subgroup of patients may be sufficiently treated on this dose. Most were prescribed 120  $\mu$ g, indicating that this is most often sufficient for NE. Treatment duration appeared to increase with increasing melt dosage, possibly due to lower numbers of reiterations in lower doses. We confirmed that severe hyponatremia is rare in children.

- O02.06 Andreas Buch  
Møller ULK1 PHOSPHORYLATION IS ALTERED BY PHYSICAL EXERCISE, FASTING, AND INSULIN IN HUMAN SKELETAL MUSCLE

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ULK1 plays a critical role in autophagic control, and the activity of ULK1 is negatively regulated by mTORC1 by phosphorylation at Ser<sup>757</sup> and

positively regulated by AMPK $\alpha$  by phosphorylation at Ser<sup>555</sup>. The aim of the present study was to investigate autophagy signaling in human skeletal muscle in response to changing energetic and nutrient demands.

Skeletal muscle biopsies from two studies in healthy human subjects were included. In the first study, subjects were investigated before and after 1 hour cycling exercise at 50% VO<sub>2</sub>-max on two occasions: 1) during 36 hours fast and 2) during continuous glucose infusion. In the second study, subjects were investigated before and during a hyperinsulinaemic euglycemic clamp during an overnight fast and 72 hours fast, respectively. Protein expression was assessed by western blot analysis.

ULK1 Ser<sup>555</sup> and AMPK $\alpha$  Thr<sup>172</sup> phosphorylation increased after exercise and the changes were positively correlated. ULK1 phosphorylation at Ser<sup>757</sup> increased during the clamp, and the changes were correlated to the changes in mTORC1 Ser<sup>2448</sup> phosphorylation. ULK1 protein expression increased after 72 hour fast, and this led to suppressed phosphorylation at and Ser<sup>757</sup>.

These results show that ULK1 phosphorylation is altered in human skeletal muscle in response to fasting and exercise, and that the changes in ULK1 phosphorylation at Ser<sup>555</sup> and Ser<sup>757</sup> is correlated to changes in AMPK $\alpha$  Thr<sup>172</sup> and mTOR Ser<sup>2448</sup> phosphorylation, respectively. Thus, signaling through ULK1 seems to integrate signals from energy and nutrient sensing enzymes to elevate autophagy in conditions of low nutrient availability, and suppress autophagy in conditions of nutrient excess.

O03.01      Mikkel Tøttrup    BONE, SUBCUTANEOUS TISSUE AND PLASMA PHARMACOKINETICS OF CEFUROXIME IN TOTAL KNEE REPLACEMENT PATIENTS - CONTINUOUS VERSUS SHORT-TERM INFUSION

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**Objectives:** The objective of this study was to describe and compare plasma, subcutaneous tissue and bone pharmacokinetics of cefuroxime after traditional short-term infusion (STI) and continuous infusion (CI).

**Methods:** Eighteen male patients undergoing total knee replacement were randomly assigned to STI or CI of 1,500 mg cefuroxime. Measurements of cefuroxime concentrations were obtained in plasma, subcutaneous tissue (SCT), cancellous and cortical bone every 30 minutes for 8 hours. For measurements in solid tissues, microdialysis was applied. Population pharmacokinetic modelling and Monte Carlo Simulations were performed in order to estimate area under the concentration-time curves (AUC), and

to assess the probability of attaining cefuroxime concentrations above the minimal inhibitory concentration (MIC) for 65% and 90% of the dosing interval.

Results: Tissue penetration was incomplete for SCT and cortical bone in the STI group. In the CI group, no decreased tissue penetration was found though cortical bone came close. No differences in AUCs and tissue penetration ratios were found between the two groups. Irrespective of tissue and target, CI leads to improved probability of target attainment (PTA) compared to STI. Nevertheless, even for the low target, high organism MICs of 8 µg/ml leads to inadequate (<90%) PTA in all tissues for both STI and CI. CI leads to adequate PTA for a MIC of 4 µg/mL in all tissues but cortical bone.

Conclusion: CI of cefuroxime is favourable compared to STI. Nonetheless, even with this approach, a standard dose of 1,500 mg leads to inadequate target attainment in all tissues for high organism MICs.

O03.02 Ane Langkilde- TRIM21 IN PSORIASIS

Lauesen  
Nielsen

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Psoriasis is considered a Th-1 and Th-17 chronic cutaneous inflammatory skin disease. Tripartite motif-containing protein (TRIM)21 is a member of the TRIM protein family, which is known to regulate transcriptional pathways in host defence. Topical application of imiquimod (IMQ), a TLR7/8 ligand and potent immune activator, can induce and exacerbate psoriasis in humans. IMQ-induced skin changes in mice are acknowledged as a mouse model for the analysis of the pathogenic mechanisms in psoriasis. However, after 4-6 days the skin changes disappear, even though application is continued. Therefore, the model can only be used as a model of early stage psoriasis.

Preliminary results have shown increased TRIM21 mRNA expression in the very early phase of IMQ-induced psoriasis-like skin inflammation in mice (5.0 fold after 2 hours) and in keratinocyte cultures stimulated with IMQ (2.5 fold after ½ hour).

From the literature, it is known that stimulation of TLR7 followed by activation of TRIM21 leads to down-regulation of IRF3 and a subsequent decrease in proinflammatory cytokine expression including IL-23p19 and type I IFN's. The short-term response of IMQ application to mice may, therefore, be due to the early upregulation of TRIM21.

We here aim to describe this pathway and characterize the response of topical application of IMQ to TRIM21 knockout mice.

O03.03 Karen Toftdahl LOCAL INFILTRATION ANALGESIA VERSUS CONTINUOUS INTERSCALENE  
Bjørnholdt BRACHIAL PLEXUS BLOCK FOR SHOULDER REPLACEMENT PAIN: A  
RANDOMIZED CLINICAL TRIAL



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Background: Shoulder replacement involves significant postoperative pain, which is often managed by continuous interscalene brachial plexus block. Catheter displacement and complications limit the beneficial effect of the block. Local infiltration analgesia (LIA) has provided good results in knee replacement. We aimed to assess the efficacy of LIA for shoulder replacement pain.

Methods: Patients scheduled for primary shoulder replacement under general anesthesia at Horsens Regional Hospital and Aarhus University Hospital, Denmark were randomized to receive either LIA: local infiltration analgesia (150 ml ropivacaine with epinephrine intra-operatively) or ISC: interscalene brachial plexus catheter (ropivacaine 0.75%, 7 ml bolus followed by 48-hour 5 ml/h infusion). The primary outcome was opioid consumption during the first 24 postoperative hours. Secondary outcomes were pain ratings, supplementary analgesics, and side effects the first three postoperative days, and complications up until 3 months after surgery.

Results: 24-hour opioid consumption was higher in the LIA group compared with the ISC group: median (IQR) 104 mg (70-150 mg) versus 40 mg (8-88 mg) ( $p = 0.0003$ ). This difference was largest in the first 3 hours (in recovery). The LIA group had higher pain scores in the first 8 hours. No difference was found in side effects, but two patients in the ISC group had long-lasting complications.

Interpretation: The described LIA technique is not recommended for analgesia after shoulder replacement. However, problems with the interscalene brachial plexus catheter technique prompt further studies in order to improve pain management after shoulder replacement.

O03.04      Lars Bo  
                 Petersen

NEUROSENSORIC DISTURBANCES AFTER SURGICAL REMOVAL OF THE LOWER THIRD MOLAR BASED ON EITHER PANORAMIC IMAGING OR CONE BEAM CT SCANNING (CBCT). A RANDOMIZED CONTROLLED TRIAL

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Background: Avoiding or reducing iatrogenic injury to the mandibular nerve in surgical removal of the lower third molar has been suggested using presurgical 3D CBCT scans. The standard-of-care is the use of 2D panoramic imaging. The aim of this study was to analyze differences in neurosensoric disturbances between a panoramic imaging group and a CBCT group in an RCT.

Methods: 220 patients were randomized to a CBCT group and a panorama group. All patients were referred from practicing dentists in the

Copenhagen area. Including criteria were overlap of the root complex and the mandibular canal on a 2D radiographic image. Central allocation of the randomization code and double blind settings were established. Surgical removal was performed in a specialized surgical practice geographically and personally separated from the study practice. Registration of neurosensoric anomalies was performed with a Semmes Weinstein test and a VAS scale questionnaire pre- and post-surgically.

Results: In the CBCT group (n=107) 19 episodes of neurosensoric disturbances were registered and in the panorama group (n=113) 13. There was no statistical significant difference between the two groups (p=0.2509). Performing a sensitivity analyses showed that if the number of patients were doubled, it would require an increase in episodes in the panorama group from 40% to 85% of the total neurosensoric disturbances before the CBCT modality could be considered superior.

Conclusion: The use of CBCT before removal of the lower third molar does not seem to reduce the number of neurosensoric disturbances.

O03.05      Jeppe Lange      VALIDITY OF HIP PROSTHESIS RELATED INFECTION DIAGNOSIS AND PROCEDURE CODES IN ADMINISTRATIVE REGISTRIES. A CROSS-SECTIONAL STUDY IN THE DANISH NATIONAL PATIENT REGISTRY FROM 2003 TO 2008

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Administrative discharge registries could be a valuable data source for research on periprosthetic hip joint infection. However, validation is necessary before use for this purpose. The aim of this study was to validate the International Classification of Disease 10<sup>th</sup> revision (ICD-10) periprosthetic hip joint infection diagnose code in an administrative discharge registry.

Patients were identified with an ICD-10 discharge diagnosis code of T84.5 (Infection and inflammatory reaction due to internal joint prosthesis) in association with hip-joint associated surgical procedure codes in The Danish National Patient Registry. Medical records of the identified patients (n=263) were reviewed and verified for the existence of a periprosthetic hip joint infection. Positive predictive values with 95% confidence intervals (95% CI) were calculated as simple proportions: the absolute number of patients with verified PJI divided by the absolute number of patients found.

A T84.5 diagnosis code, irrespective of the associated surgical procedure code, had a positive predictive value of 84% (95% CI: 79-88). Stratified to T84.5 in combination with an infection-specific surgical procedure code the positive predictive value increased to 87% (95% CI: 81-92), and in combination with a noninfection-specific surgical procedure code

decreased to 80% (95% CI: 72-87).

A certain degree of misclassification must be expected and taken into consideration when using administrative discharge registries for epidemiological research. However, we believe that the periprosthetic hip joint infection diagnose code in administrative discharge registries is very suitable for use in future register-based studies.

O03.06      Line Raaby      CHANGES IN MRNA EXPRESSION PRECEDE CHANGES IN MIRNA  
Steenberg      EXPRESSION IN LESIONAL PSORIATIC SKIN DURING TREATMENT WITH  
ADALIMUMAB

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Tumour necrosis factor (TNF)- $\alpha$  inhibitors are an effective treatment for moderate to severe plaque-type psoriasis. A change in the cytokine expression profile occurs in the skin after four days of treatment preceding any clinical or histological improvements. MicroRNAs (miRNAs) are important post-transcriptional regulators of gene expression and known to be dysregulated in psoriasis.

The aim was to investigate changes in miRNA expression in psoriatic skin during adalimumab treatment and to study the relationship between TNF- $\alpha$  and miRNA in the early phases of psoriasis in a mouse model.

Punch biopsies from psoriatic patients were collected before and 4 and 14 days after adalimumab initiation. Skin-inflammation in TNF- $\alpha$  knock out (KO) and wild type mice (wt) was induced with Aldara. miRNA expression was measured with microarray, RT-qPCR and in situ hybridisation.

No changes in the expression level in any of the ~400 investigated miRNAs were seen after four days of adalimumab treatment. After 14 days of treatment, the expression of 22 miRNAs was changed towards the level seen in untreated nonlesional skin. Aldara-induced skin inflammation increased the level of miR-146a, whereas no regulation was seen for miR-203, miR-214-3p, miR-125a, miR-23b or let-7d-5p in neither wt nor in TNF- $\alpha$  KO mice.

The changes seen in the mRNA cytokine expression profile after four days of adalimumab treatment are, therefore, not likely facilitated by early changes in miRNA expression. Furthermore, the changes in miRNA expression seen after 14 days of treatment are more likely a result of disease improvement rather than of a direct TNF- $\alpha$  inhibition, as limited regulation was seen in TNF- $\alpha$  KO mice.

O04.01      Simon Gabriel      ROLE OF SK<sub>3</sub>CHANNELS IN ERECTILE FUNCTION IN MICE  
Comerma      *S. Comerma-Steffensen<sup>1</sup>, A. Kun<sup>1</sup>, E. Hedegaard<sup>1</sup>, S. Mogensen<sup>1</sup>, C.*  
Steffensen      *Aalkjaer<sup>2</sup>, R. Kohler<sup>3</sup>, B. Mønster Christensen<sup>4</sup>, U. Simonsen<sup>1</sup>*

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Cardiovascular disease and erectile dysfunction are associated, sharing the same risk factors, and are probably linked by endothelial dysfunction. The role of these channels in erectile function has not been addressed. The present study hypothesized that small conductance calcium-activated K<sup>+</sup> channels (KCa<sub>2.3</sub> or SK<sub>3</sub>) contribute to erectile function. This was examined in mice with either overexpression (SK<sub>3</sub><sup>+/+</sup>) or downregulation (SK<sub>3</sub><sup>-/-</sup>) of the SK<sub>3</sub> channels and wild-type C57Bl/6 mice (WT). The mean arterial pressure (MAP) and the intracavernosal pressure (ICP) were measured in anaesthetized animals, corpus cavernosum strips were mounted for isometric tension recording, besides tissue were processed for immunohistochemistry, using a SK<sub>3</sub> antibody. MAP was decreased in SK<sub>3</sub><sup>+/+</sup> mice compared with WT and SK<sub>3</sub><sup>-/-</sup> mice. Stimulation of the cavernous nerve caused frequency-dependent increases in erectile function measured as ICP/MAP, and these responses were markedly decreased in SK<sub>3</sub><sup>-/-</sup> mice compared with WT and SK<sub>3</sub><sup>+/+</sup> mice. An opener of SK<sub>3</sub> and intermediate conductance calcium-activated K<sup>+</sup> channels (IK or KCa<sub>3.1</sub>), NS309 induced concentration-dependent relaxations, which were enhanced in the corpus cavernosum from SK<sub>3</sub><sup>+/+</sup> versus SK<sub>3</sub><sup>-/-</sup> mice, while responses to the NO donor sodium nitroprusside (SNP) were unaltered. Additionally, immunoblotting and immunohistochemistry revealed, that SK<sub>3</sub> channels are expressed in corpus cavernosum samples from C57Bl/6 mice. Our findings suggest that downregulation of SK<sub>3</sub> channels affects erectile function, and that opening of these channels may restore erectile function in disease.

O04.02 Lone Winther AUTOIMMUNE DISEASES AND BREAST CANCER RECURRENCE:  
Lietzen A DANISH NATIONWIDE PROSPECTIVE COHORT STUDY

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Background: Autoimmune diseases (AD) comprise a large group of heterogeneous diseases in which immune function is misdirected to attack healthy organs. Both intrinsic changes in the body and treatment of AD can compromise immune function. Such impaired immune function could influence the risk of recurrent cancer. This hypothesis has not been investigated in a large epidemiological study.

Method: This population-based cohort study examined the risk of breast cancer (BC) recurrence associated with an AD diagnosis among incident stage I-III BC patients diagnosed 1980-2007. Data were obtained from Danish population-based medical registries. ADs were categorized dichotomously and according to organ system of origin. Women were followed for up to 10 years or until 31 December 2009. Multivariate Cox

proportional hazard regressions to compute hazard ratios (HR) and associated 95% confidence intervals (95% CI) were used to evaluate the association between AD diagnosis and recurrence.

Results: 78,095 women with stage I-III BC were enrolled. Mean age 61 years (range 19-102); mean follow-up 6.2 years; 13,545 developed recurrences during follow-up. 6,716 women had at least one AD. In adjusted models, women with ADs had a near-null association with risk of BC recurrence:  $HR_{adjusted}=0.96$  (95%CI: 0.89, 1.04). In subcategories of ADs the near-null results were robust to stratification except for the central nervous/ neuromuscular system category with  $HR_{adjusted}$ : 0.56 (95% CI 0.40, 0.78).

Conclusion: Having at least one AD diagnosis is not associated with BC recurrences; with the possible exception of ADs that affect the central nervous and neuromuscular system.

O04.03      Johannes      PRE-TREATMENT COMPONENT SPECIFIC IGE DETERMINES THE IGG4  
Martin Schmid      RESPONSE UNDER THE UPDOSING PHASE OF SUBCUTANEOUS  
IMMUNOTHERAPY WITH TIMOTHY GRASS POLLEN EXTRACT

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Background: Grass pollen immunotherapy is an effective treatment of allergic rhino-conjunctivitis. We studied changes in allergen component specific immunoglobulins occurring during the up dosing of subcutaneous immunotherapy (SCIT).

Objective: To study the changes of allergen specific IgE and IgG4 on a component resolved level.

Methods: Twenty-four subjects with grass pollen allergic rhino-conjunctivitis were randomised 3:1 to receive SCIT (Alutard SQ) or to an open control group. Allergen component specific IgE and IgG4 concentrations were measured by 2 different methods (ISAC and CAP) at baseline and after 12 weeks, when reaching maintenance dose of SCIT.

Results: Grass pollen specific immunotherapy induced a strong component specific IgG4 increase from a median of 0 ISU at baseline to 0.83 ISU after 12 weeks ( $p<0.0001$ ,  $n=102$ ). IgE decreased correspondingly from a median 4.60 ISU to 2.14 ISU ( $p<0.0001$ ,  $n=102$ ) when measured by ISAC. The induction of IgG4 during up dosing depended strongly on the pre-treatment allergen component specific IgE.

Conclusion: Pre-treatment allergen component specific IgE predicts the induction of IgG4, resulting in a strong correlation between the pre-treatment IgE level and the post-up dosing IgG4 concentrations. The induced IgG4 has the ability to suppress measurement of IgE on the ISAC chip, resulting in a marked decrease in allergen specific IgE during the

up dosing of SCIT in grass pollen allergic patients.

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|--------|-----------------------------------|---|
| O04.04 | Niels<br>Bjerregård<br>Matthiesen | <p>CONGENITAL HEART DISEASE AND HEAD CIRCUMFERENCE AT BIRTH: A DANISH POPULATION-BASED COHORT STUDY OF CHILDREN WITH DOWN SYNDROME</p> <p><i>N.B. Matthiesen<sup>1</sup>, V. Hjortdal<sup>2</sup>, P. Agergaard<sup>1</sup>, J.W. Gaynor<sup>2</sup>, T.B. Henriksen<sup>1</sup>, J.R. Østergaard<sup>1</sup></i></p> <p><sup>1</sup>Department of Paediatrics, Aarhus University Hospital, <sup>2</sup>Division of Cardiothoracic Surgery, The Children's Hospital of Philadelphia, <sup>3</sup>Dept. of Cardiothoracic and Vascular Surgery, Aarhus University Hospital</p> <p>Background and aims: Neurodevelopmental disorders are frequent in children with congenital heart disease (CHD). These disorders have been attributed to prenatal factors such as impaired cerebral growth. Down syndrome (DS) is a known cause of CHD, neurodevelopmental disorders and microcephaly. Hence, studies on DS may provide insight in to the causes of impaired cerebral growth in CHD. We aimed to estimate the association between CHD and head circumference at birth in a large cohort of children with DS.</p> <p>Methods: Children with DS (n=726) and specific birth characteristics were identified in national registries. Head circumference, cephalization index and microcephaly at birth (head circumference &lt;-2SD) were compared between children with CHD (n=298) and children without CHD (n=372) by linear and logistic regression analyses. The exposure was further restricted to children with severe CHD (n=103).</p> <p>Results: There was no association between CHD and any measure of head circumference at birth. Head circumference z-score: -0.1(95%CI, -0.2; 0.1), cephalization index z-score: 0.1(95%CI, -0.1; 0.2), odds ratio of microcephaly: 1.4 (95%CI, 0.8; 2.4). The estimates were the same, when the exposure was restricted to severe CHD.</p> <p>Conclusions: We found no association between CHD and head circumference at birth in a large cohort of children with DS. Even severe CHD was not associated with head circumference at birth. We suggest that previous findings of smaller head circumferences at birth in isolated CHD may have been due to unknown genetic causes rather than CHD itself.</p> |
| O04.05 | Ninna<br>Aggerholm-<br>Pedersen   | <p>THE INFLUENCE OF HYPOXIA ON SARCOMA PATIENT'S RESISTANCE TO CHEMOTHERAPY</p> <p><i>N. Aggerholm-Pedersen<sup>1</sup>, A. Safwat<sup>2</sup>, S. Bærentzen<sup>3</sup>, M. Nordmark<sup>2</sup>, O. Steen Nielsen<sup>4</sup>, J. Alsner<sup>1</sup>, B. Sørensen<sup>1</sup></i></p> <p><sup>1</sup>Department of Experimental Clinical Oncology, Aarhus University Hospital, <sup>2</sup>Department of Oncology, Aarhus University Hospital, <sup>3</sup>Department of Pathology, Aarhus University Hospital, <sup>4</sup>Faculty of Health, Aarhus University</p>  |

The prognosis of sarcoma patients is poor due to poor response to chemotherapy, maybe because of hypoxia inside the tumors. The material often-available are routinely collected formalin-fixed, paraffin embedded (FFPE) samples in which the mRNA is highly degraded and the choice of reference genes is of paramount importance as it is essential for correct interpretation of data. The aim of the present study was to identify a hypoxia induced gene profile in human sarcoma and to investigate the impact of this profile on overall survival.

Methods: A hypoxia induced gene profile found in head and neck cancer were teste in retrospectively collected diagnostic biopsies from sarcoma patients (cohort 1: 30 patients) by qPCR. The gene profile correlation to oxygen tension measurement from the inside the tumor were tested. A cohort of 60 sarcoma patients selected from the sarcoma database was matched to cohort 1, and the prognostic role of the gene profile was tested. Primary endpoints were overall survival.

Results: PPIA, SF3A1 and MRPL19 are suitable reference genes for normalization in gene expression studies of FFPE samples from sarcoma regardless of the histology and these genes could compensate for the time dependent degradation of mRNA. The oxygen tension measurement inside the tumors and the expression of the gene profile correlated well. The results are to be analyzed for the prognostic role for the gene profile.

Conclusion/perspectives: The gene profile found in head and neck cancer may be a universal classifier of other cancers. If the profile correlates with overall survival of the patient, targeting hypoxia could be a new treatment modality for sarcoma patients.

O04.06 Søs Ann  
Christine  
Neergaard-  
Petersen

HYPERGLYCAEMIA IS ASSOCIATED WITH A REDUCED ANTIPLATELET EFFECT OF ASPIRIN IN PATIENTS WITH CORONARY ARTERY DISEASE

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Background and aim: Low-dose aspirin reduces the risk of cardiovascular events. However, the antiplatelet effect of aspirin is reduced in patients with coronary artery disease (CAD) and concomitant diabetes. Thus, we investigated the influence of hyperglycaemia on platelet turnover and platelet aggregation in patients with CAD.

Methods: We included 865 patients with CAD on aspirin mono-therapy (75 mg daily). Among these, 28% had diagnosed type 2 diabetes. Levels of glycaemia were evaluated by haemoglobin A1c (HbA1c), and prediabetes was defined as HbA1c  $\geq 5.7$ -6.4%. Platelet turnover was evaluated by immature platelets using flow cytometry (Sysmex XE-2100); platelet activation by soluble P-selectin (ELISA); platelet aggregation by Multiplate® aggregometry using arachidonic acid and collagen and the VerifyNow® Aspirin. Compliance to aspirin was verified by serum thromboxane B<sub>2</sub>.

Results: Levels of HbA1c correlated positively with immature platelet count ( $r = 0.13$ ,  $p < 0.001$ ); soluble P-selectin ( $r = 0.14$ ,  $p < 0.0001$ ); collagen- ( $r = 0.20$ ,  $p < 0.001$ ) and arachidonic acid-induced platelet aggregation ( $r = 0.12$ - $0.20$ ,  $p < 0.001$ ) and the VerifyNow® ( $r = 0.14$ ,  $p < 0.0001$ ). Among patients without known diabetes ( $n = 623$ ),  $n = 303$  (49%) had prediabetes and correlations were strongest in these patients. All patients were compliant with aspirin confirmed by serum thromboxane B<sub>2</sub> levels below 27 ng/mL.

Conclusion: Hyperglycaemia is associated with increased levels of platelet turnover, platelet activation and platelet aggregation. This association is strongest in CAD patients with prediabetes. Thus, hyperglycaemia may attenuate the antiplatelet effect of aspirin in patients with CAD.

O05.01 Henrique  
Fernandes

# STRUCTURAL BRAIN CONNECTIVITY FINGERPRINTING AS A NEW PRE-SURGICAL TOOL FOR DEEP BRAIN STIMULATION TARGET DISCOVERY

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Synchronization of neural oscillations has been suggested to be an important principle of regulating network communication, serving as an important mechanism for unravelling neural assemblies and their functional roles. Deep brain stimulation (DBS) targeting has been the product of carefully utilizing animal models but has also been the result of serendipity during human lesional neurosurgery. There are, however, no good animal models of psychiatric disorders such as depression and schizophrenia and progress in this area has been slow.

In this study, we use advanced tractography combined with whole-brain anatomical parcellation and to provide a rational foundation for identifying the structural connectivity 'fingerprint' of existing, successful DBS targets. First, using data from our recent case series of cingulate DBS for patients with treatment-resistant chronic pain, we demonstrate how to identify the structural 'fingerprints' of existing successful and unsuccessful DBS targets. Second, we used different strategies to characterize and compare the fingerprints of structural connectivity between the two groups.

This fingerprinting method can potentially be used pre-surgically to account for the patient's individual connectivity and identify the most effective DBS target. The identification of neural signatures of pathological brain activity will provide new insights and potentially the discovery of new targets that will best modulate the balance of the brain in hitherto impenetrable neuropsychiatric disorders.



O05.02      Anders Riisager EFFECTS OF THE PKC-INDUCED PHOSPHORYLATION ON THE FAST- AND COMMON GATING OF THE MUSCLE SPECIFIC CLC-1 CHLORIDE CHANNEL

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The voltage gated CLC-1 chloride channel is a homodimer in which the current is governed by individual fast gates in each channel pore and by a common slow gate. In skeletal muscle, where the channels are abundantly expressed in the cell membrane, they contribute to the maintenance of the resting membrane potential and to its restoration after excitation by shunting current required for the initiation and propagation of action potentials. Recent studies on human and rodent muscle shows that the onset of muscle activity induces an up to 60 % down-regulation of the currents carried through CLC-1 at the resting membrane potential, which serves to fine tuning the excitability of the muscles during continued activity. While it has been identified that this regulation is caused by PKC dependent phosphorylation, the changes in the gating of the channels leading to this regulation remains unknown.

Aim: This study thus aimed to investigate the changes in CLC-1 gating in response to PKC dependent phosphorylation.

Methods: Human CLC-1 channels were expressed in *Xenopus laevis* oocytes and their current-voltage relationship characterized by two electrode voltage clamp. PKC was activated by PMA. Control experiments were carried out using the inactive analogue 4- $\alpha$ -PDD or the specific PKC inhibitor GF109203X.

Results: The expressed CLC-1 channels showed a large rightward shift in the current-voltage relationship when PKC was activated by PMA, shifting the half activation voltage from -90 to -35 mV, while no shift was seen in control experiments. Preliminary data further suggest that the PKC primarily alters the common gate of the channels while the fast gating was less affected.

O05.03      Gitte Bundgaard Christiansen THE ROLE OF THE POSTSYNAPTIC RECEPTOR SORCS3 IN SYNAPTIC PLASTICITY AND SYNAPTIC TRANSMISSION

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SORCS3 (sortilin-related receptor CNS expressed 3) is a member of the VPS10P-domain receptor gene family. Other family members have been shown to be involved in synaptic plasticity and different disorders of the CNS. The neuronal receptor SORCS3 is expressed postsynaptically in the CA1 area of the hippocampus and we have therefore performed electro-

physiological recordings in this area. More precisely, we took advantage of extracellular field recordings in acutely isolated brain tissue of a SORCS3-deficient mouse model, in order to study the role of SORCS3 in synaptic plasticity and synaptic transmission.

We have recently shown that SORCS3 is important for two forms of long-term depression (LTD) called NMDAR-dependent and mGluR-dependent LTD. Furthermore, we have shown that the early phase of long-term potentiation (LTP) is normal and that there is no difference in the ratio of paired-pulse facilitation (Breiderhoff et al., 2013). These data indicate that SORCS3 plays an important postsynaptic role in long-term depression which is an essential type of synaptic plasticity. To further characterize the role of SORCS3 we have performed input/output-curves. Data from these input/output-curves indicate that synaptic transmission in SORCS3-deficient mice is changed compared to wild-types.

Taken together, these data have revealed that SORCS3 is a key player in synaptic plasticity and synaptic transmission. We believe that SORCS3 plays a vital role in the mechanisms underlying LTD, most likely in the removal and/or retention of AMPA receptors from the postsynaptic density which is important during LTD.

O05.04 Baris Isak

#### INVOLVEMENT OF A-BETA SENSORY FIBRES IN AMYOTROPHIC LATERAL SCLEROSIS

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Background: Amyotrophic lateral sclerosis (ALS), termed as motor neuron disorder, is a disease involving mainly upper and lower motor neurons. As a general approach, detection of any sensory abnormality in nerve conduction studies (NCSs) leads the physician to exclude ALS. However, increasing evidence suggest that ALS is a multisystem disorder that also involves the sensory nerves.

Objective: In this study, we wanted to see if distal and proximal large diameter sensory nerves (A-beta fibres) were deteriorated in ALS.

Methods: We recruited 15 definite-ALS patients based on El-Escorial criteria to compare with 27 healthy subjects. We recorded distal sensory NCSs [i.e., dorsal sural (DS) and medial plantar (MP)] in addition to standardized proximal sensory NCSs [i.e., unilateral median sensory and bilateral sural (SU) nerves] in both groups. Also, somatosensory evoked potentials (SEPs) in upper (UE-) and lower extremities (LE-) were recorded.

Results: ALS patients had several deteriorations in standardized sensory NCSs (abnormal median sensory- and right SU-NCS in 1 and 4 patients, respectively). Also, we recorded abnormal DS-NCSs (9 patients bilaterally

and 3 patients unilaterally) and MP-NCSs (6 patients bilaterally and 1 patient unilaterally) in ALS patients. UE- and LE-SEPs were abnormal in 5 and 7 patients, respectively.

Conclusions: Lemniscal tract seems to be involved in ALS progression as well as corticospinal tract. We saw that distal sensory NCSs deteriorated earlier and more severe than the proximal sensory NCSs in ALS. Hence, detection of any abnormality in sensory NCSs does not rule out the diagnosis of ALS.

O05.05 Janne  
Kærgård  
Mortensen

#### ALL-CAUSE 30-DAY MORTALITY RELATED TO POST-STROKE ANTI-DEPRESSANT TREATMENT

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Background and aim: Antidepressants may mediate stroke outcome by having additional antithrombotic and neuroprotective properties. We aimed to examine 30-day mortality related to early antidepressant treatment after ischemic stroke.

Methods: Using information from Danish medical registries we did a population-based follow-up study from 2003-2010. Multivariable logistic regression was used to compute the adjusted odds ratio of 30-day mortality among patients treated with antidepressants during admission as compared to patients not treated. In addition, a propensity score matched (1:1) adjusted odds ratio of 30-day mortality was computed and finally stratified analyses on sex, age and stroke severity were done.

Results: Among 5070 consecutive first ever stroke patients without prior antidepressant treatment, 955 (18.8%) started antidepressant treatment during admission with a median time before treatment of 5 days (inter-quartile range: 2-11). The adjusted odds ratio of death was 0.27 (95% CI: 0.17-0.43) for patients treated during admission as compared to patients not treated during admission. The propensity score matched adjusted odds ratio of death was 0.31 (95% CI: 0.19-0.49). In the stratified analyses the association between treatment and reduced mortality was strongest among the most severe strokes. Overall the treated patients had more severe strokes.

Conclusion: Although early antidepressant treatment was associated with more severe strokes, treatment was also associated with significantly lower mortality.

O05.06 Christina  
Sølvsten

#### NEURONAL EPIGENETIC ALTERATIONS INDUCED BY PHYSICAL EXERCISE

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Any identified relevant epigenetic modifications and the response genes will further on be functionally examined in neuronal cell models by molecular and cellular methods.

Aim of the project: The aim is to clarify whether the ROTEM® (Tem International GmbH) analysis is significantly influenced by antithrombotic medicine or whether this medication will be overlooked when performing the ROTEM®-analysis.

Methods: Two hundred and ten patients on antithrombotic therapy will be included from October 2014; 70 patients receiving vitamin K-antagonist (INR 2-3), 70 patients receiving aspirin and 70 patients receiving aspirin and ADP-inhibitor. Whole blood coagulation is assessed by ROTEM®-analysis using the three standard assays INTEM, EXTEM and FIBTEM. Additionally APTT, INR, platelet count, haemoglobin, fibrinogen (functional), creatinine and CRP are analysed. Serum-Thromboxane B2 will be determined and used as compliance control for patients receiving aspirin. The results from the ROTEM®-analysis will be compared with known data from healthy subjects.

Results: Data are currently being collected and the initial results will be presented at the congress.

- P01.02      Simon Graff      LONG-TERM RISK OF ATRIAL FIBRILLATION AFTER THE DEATH OF A SPOUSE: A NATIONWIDE POPULATION-BASED CASE-CONTROL STUDY
- S. Graff<sup>1</sup>, M. Fenger-Grøn<sup>1</sup>, B. Christensen<sup>2</sup>, H.S. Pedersen<sup>1</sup>, J. Christensen<sup>3</sup>, J. Li<sup>4</sup>, M. Vestergaard<sup>1,2</sup>*

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Background: The impact of psychological stress on the risk of developing atrial fibrillation (AF) remains unclear. We examined whether the loss of a spouse was associated with AF.

Methods: We conducted a population-based case-control study by using nationwide health registers in Denmark. Between 1995 and 2013, we identified 171.796 cases with a hospital diagnosis of AF and 1.717.960 age and sex matched controls based on risk-set sampling. We used conditional logistic regression to calculate odds ratios (ORs) with 95% confidence intervals (CI).

Results: During the study period, 46.376 cases and 453.646 controls were exposed to spousal bereavement. Bereavement was followed by a transient higher risk for AF; the risk was the highest 8-14 days after the loss of a spouse (1.66; 95% CI 1.29-2.13), thereafter it gradually declined to a level close to that for the non-bereaved one year after the loss. Overall, the OR of AF within 30-days of the bereavement was 1.30 (95% CI 1.14-1.48) but it tended to be higher among persons younger than 60 years (1.56; 95% CI 0.85-2.87) and persons who lost a healthy spouse i.e. a low Age-adjusted Charlson Comorbidity Index (ACCI) (1.88; 95% CI 1.10-3.21).

Conclusions: Spousal bereavement was followed by a transient higher risk of AF lasting for one year, especially if the loss was unexpected.

- P01.03      Thomas Lyngaa      VARIATION OF INTENSIVE CARE UTILIZATION AT THE END-OF-LIFE IN PATIENTS DYING FROM CHRONIC NON-CANCER DISEASE VERSUS CANCER: A NATIONWIDE CROSS-SECTIONAL STUDY
- T. Lyngaa<sup>1</sup>, C.F. Christiansen<sup>1</sup>, H. Nielsen<sup>1</sup>, M.A. Neergaard<sup>2</sup>, A.B. Jensen<sup>3</sup>, K.G. Lauf<sup>4</sup>, S.P. Johnsen<sup>1</sup>*
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- Background: Intensive care is often provided towards end-of-life (EOL), occupying resources and causing emotional burden for patients while not necessarily aligning with their preferences.
- Aim: To examine if age, sex and underlying chronic disease (UCD) predict use of intensive care at the EOL.
- Methods: Nationwide historical cross-sectional study of all 240,757 adults dying of cancer or chronic non-cancer (NC) disease (diabetes, dementia, ischemic heart disease, heart failure, chronic obstructive pulmonary disease (COPD), stroke, and chronic liver failure) in Denmark from 2007-2011. Using the Danish Intensive Care Database, we identified all admissions to intensive care units (ICU) the last 6 months before death. We calculated proportions and compared adjusted risk ratios (aRR) for ICU admission according to age, gender and UCD in cancer and NC patients.
- Results: Overall, 12.3% of NC patients were admitted to ICU within their last 6 months. For cancer patients, this was 8.7%. Overall aRR for ICU admission at EOL in NC patients was 2.11(95%CI: 1.98-2.24). Patients with dementia had an aRR 0.19 (95%CI: 0.17-0.21), and COPD patients an aRR 3.19 (95%CI: 2.97-3.41) for ICU admission, compared to cancer patients. Among patients aged 90+, NC patients were less likely to be admitted to an ICU compared to cancer patients (aRR women 0.60(95%CI: 0.50-0.73), aRR men 0.85(95%CI: 0.65-1.11))
- Conclusion: The variation in use of intensive care at EOL in patients with chronic disease warrant further investigation into the interaction between patients' needs and preferences, and prioritization of resources.
- P01.04      Anne Katrine Wulff Nielsen      IS HAEMOSTASIS IMPAIRED IN CARDIAC ARREST PATIENTS DURING THERAPEUTIC HYPOTHEMIA?
- A.K. Wulff Nielsen<sup>2</sup>, A. Nørgaard Jeppesen<sup>2</sup>, H. Kirkegaard<sup>2</sup>, A.M. Hvas<sup>1</sup>*
- <sup>1</sup>Centre for Haemophilia and Thrombosis, Department of Clinical Biochemistry, Aarhus University Hospital, <sup>2</sup>Research Centre for Emergency Medicine, Aarhus University Hospital
- Background: Therapeutic hypothermia improves neurological outcome in patients resuscitated after cardiac arrest. The impact on haemostasis during therapeutic hypothermia has not yet been fully investigated.

Hypothesis and aim: Our hypothesis was that clotting time was significantly longer during hypothermia compared to normothermia. We aimed to investigate the haemostatic changes during hypothermia.

Methods: We included cardiac arrest patients admitted to Aarhus University Hospital, Skejby and treated with hypothermia ( $33\pm 1^{\circ}\text{C}$ ) for 24-48 hours from January-August 2014. Blood were sampled 3 times with intervals of 24 hours. Blood samples were obtained using citrated tubes and rested for 30 minutes. Clotting time was detected with thromboelastometry (ROTEM®, Tem International GmbH) using a sensitive low-tissue-factor assay to trigger coagulation. Tissue factor (Innovin®) was diluted in calcified buffer providing a final dilution at 1:50.000 in the ROTEM cup. Additionally, haemostasis was evaluated by standard coagulation analyses; platelet count, international normalised ratio, activated partial thromboplastin time, thrombin time, fibrinogen and haemoglobin.

Results: We included 27 patients. Data are currently being analysed. Main endpoint is clotting time obtained by analyses on ROTEM® using a low-tissue-factor assay, in addition, clot formation and strength will be presented. Besides the dynamic coagulation parameters, results from the standard coagulation analyses obtained at hypothermia and normothermia respectively will be presented.

Conclusion: We hope to clarify whether haemostasis is significantly impaired in cardiac arrest patients during therapeutic hypothermia.

P01.05      Sidse Høst  
Pahus

THROMBOPHILIA IS NOT MORE PREVALENT IN YOUNG PATIENTS WITH ISCHEMIC STROKE THAN IN THE GENERAL POPULATION

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Background: In young patients with ischemic stroke classical risk factors for atherosclerosis are rarely identified and the role of thrombophilia as regards ischemic stroke is controversial.

Hypothesis: We hypothesized that the prevalence of thrombophilia was higher in patients with ischemic stroke or a transient ischemic attack (TIA) with onset before 50 years of age compared to the general population.

Methods: This was a retrospective observational study including patients with ischemic stroke or TIA diagnosed at age 18 to 50 years and referred to thrombophilia investigation at Centre of Haemophilia and Thrombosis, Aarhus University Hospital from 2004 to 2013. Clinical information was obtained from the Danish Stroke Registry. Additional clinical information was systematically collected from medical records. Data from thrombophilia investigations were obtained from the laboratory information system LABKA I and II.

Results: The study population consisted of 766 patients with ischemic stroke (n=292), TIA or Amarosis Fugax. These preliminary results contain only

ischemic stroke patients. Heterozygosity of a Factor V Leiden mutation was found in 10 (6%) patients and heterozygosity for the prothrombin 20310 G:A mutation in 1 (2%) patient. Antithrombin deficiency or Protein C deficiency was not found in any patients. Protein S deficiency was diagnosed in 3 (1%) patients. Lupus anticoagulant was positive in 5 (2%) patients.

Conclusion: The prevalence of thrombophilia was not increased in young ischemic stroke patients as compared to the general population. This finding supports the Danish recommendations recommending no systematic thrombophilia testing after ischemic stroke.

P01.06      Emil Vibede      THE EFFECT OF FRESH FROZEN PLASMA IN CRITICALLY ILL PATIENTS

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Background: Fresh frozen plasma (FFP) is often used to treat critically ill patients because it provides coagulation factors and thereby potentially reduces the risk of bleeding. The indication of FFP transfusion is primarily based on abnormal conventional coagulation tests, but the evidence for this strategy is limited. Importantly, transfusion of FFP implies risk of infections and transfusion-related acute lung injury (TRALI).

Aim: To clarify if thromboelastometry (ROTEM®) improves the decision-making prior to FFP transfusion compared to the use of conventional coagulation tests alone. Further, we investigate the incidence of symptoms of TRALI.

Methods: We plan to include 50 patients at the Department of Intensive Care, Aarhus University Hospital, who receive a minimum of two portions FFP during admission. Blood samples are obtained prior to FFP transfusion, and 1 hour after the last transfusion. Besides thromboelastometry (ROTEM®), conventional coagulation and haematological tests (PP, INR, APTT, fibrinogen (functional), antithrombin, haemoglobin and platelets) and thrombin generation are preformed. The clinical state of the patient is assessed with intensive care unit scoring systems. For every patient receiving FFP, a control patient is included and clinical data regarding TRALI are obtained for both groups.

Conclusion: We expect to clarify whether the use of ROTEM® improves the decision making as regards FFP transfusion in critically ill patients.

Perspectives: Potentially, this study will help to improve diagnosis in and treatment quality of critically ill patients with a concomitant reduction in the risk of transfusion related side effects.



P01.07	Jacobina Kristiansen	<p>THE EFFECT OF REMOTE ISCHAEMIC PRECONDITIONING ON CLOT FORMATION AND DEGRADATION</p> <p><i>J. Kristiansen<sup>1</sup>, N. Rise<sup>1</sup>, S.D. Kristensen<sup>1</sup>, E.L. Grove<sup>1</sup>, S. Neergaard-Petersen<sup>1</sup>, M. Würtz<sup>2</sup>, A.M. Hvas<sup>3</sup></i></p> <p><sup>1</sup>Department of Cardiology, Aarhus University Hospital, <sup>2</sup>Department of Internal Medicine, Regional Hospital West Jutland, Denmark, <sup>3</sup>Department of Clinical Biochemistry, Aarhus University Hospital</p> <p>Background: Remote ischaemic preconditioning (RIPC) reduces infarct size and improves prognosis in patients with acute myocardial infarction. However, the underlying mechanisms of these beneficial effects are unknown.</p> <p>Aim: To investigate the effect of RIPC on the formation and degradation of blood clots.</p> <p>Methods: In this observational cross-over study, we will include 30 healthy participants who will visit the hospital three times. At first visit (day 1), participants are exposed to a sham ("placebo") intervention. At second (day 2) and third (day 16) visit, they are exposed to RIPC (intermittent arm ischaemia through four cycles of 5-minutes inflation of a blood-pressure cuff followed by 5-minutes deflation). Prior to the third visit, all participants will be treated with aspirin for seven days. Blood samples will be obtained at baseline (before RIPC) as well as 5 and 45 minutes after sham/RIPC. We will investigate changes in whole blood coagulation with thromboelastometry (ROTEM®) and fibrin clot lysis with a turbidimetric clot lysis assay. Participants will be recruited from the 1<sup>st</sup> November 2014.</p> <p>Results: Will be presented at the congress. We expect to find decreased clot formation evaluated by clotting time and maximum clot firmness (ROTEM®) and increased clot degradation evaluated by clot lysis time (clot lysis assay), when comparing blood samples obtained at baseline with blood samples obtained after RIPC.</p> <p>Perspectives: The study will increase our knowledge about the mechanisms underlying the beneficial effects of RIPC. This knowledge is important for the potential implementation of RIPC as routine care in patients with acute myocardial infarction.</p>
P01.08	Nina Rise	<p>THE EFFECT OF REMOTE ISCHEMIC PRECONDITIONING ON PLATELET FUNCTION AND PLATELET TURNOVER</p> <p><i>N. Rise<sup>1</sup>, J. Kristiansen<sup>1</sup>, E.L. Grove<sup>1</sup>, M. Würtz<sup>1,2</sup>, S. Neergaard-Petersen<sup>1</sup>, A.M. Hvas<sup>3</sup>, S.D. Kristensen<sup>1</sup></i></p> <p><sup>1</sup>Department of Cardiology, Aarhus University Hospital, <sup>2</sup>Department of</p>

Internal Medicine, Regional Hospital West Jutland, Denmark, <sup>3</sup>Department of Clinical Biochemistry, Aarhus University Hospital

Background: Remote ischemic preconditioning (RIPC) is a new treatment that reduces infarct size and improves long-term prognosis in patients with ST-elevation myocardial infarction. The mechanisms behind this advantageous effect are poorly understood, but the benefit of RIPC may represent a direct effect on platelet function and platelet turnover, which is inhibited by antiplatelet drugs such as aspirin.

Objective: To investigate the effect of RIPC on platelet function and platelet turnover.

Methods: 30 healthy males will be included in an observational cross-over study. They will be subjected to RIPC as follows: 1st visit (day 1): Sham intervention, off aspirin 2nd visit (day 2): RIPC intervention, off aspirin 3rd visit (day 16): RIPC intervention, on aspirin During RIPC, harmless episodes of ischemia are induced by inflating a blood pressure cuff around an arm for 5 minutes followed by 5 minutes of deflation. This cycle is repeated four times. Blood samples are drawn five minutes prior to the intervention as well as 5 and 45 minutes after the intervention. Platelet function will be measured using Multiplate<sup>®</sup> Analyzer and platelet turnover will be measured using Sysmex<sup>®</sup> XE-5000.

Results: Not yet available. Data will be collected from 1<sup>st</sup> November 2014. We hypothesize that RIPC reduces platelet function and platelet turnover.

Perspectives: This study will provide new insight into the link between RIPC and platelet function, both off and on aspirin. Aspirin treatment is crucial, as optimal clinical benefit from RIPC can only be achieved if combined with standard antiplatelet treatment.

P01.09      Musa Kaya      THE EFFECT OF CHANGES IN PROSTAGLANDIN AND NO LEVELS ON DIAMETER CHANGES IN RETINAL VESSELS DURING HYPOXIA

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Purpose: Retinal hypoxia with consequent changes in blood flow is essential in common vision-threatening diseases. The aim of this study was to examine the effect of a nitric oxide (NO) donor and inhibition of COX-products on the changes of retinal vessel diameters during hypoxia.

Methods: Twenty healthy persons aged 20-47 years were examined using the Dynamic Vessel Analyzer (DVA) with measurements of retinal vessel diameters during rest, isometric exercise and flicker stimulation. The measurements were performed during normoxia and hypoxia before and after sublingual administration of the NO donor nitroglycerine, and were repeated on a second study day after topical administration of the COX-inhibitor diclofenac.

Results: The resting diameter of the arterioles and venules increased

significantly during hypoxia alone and in combination with nitroglycerine ( $p < 0.0001$ ). The gain factor (GF) was found not to differ significantly from 1 in any of the interventions, indicating that the blood flow did not change. Hypoxia alone and combined with nitroglycerine significantly reduced both the arteriolar contraction during isometric exercise and the dilatation of the arterioles and venules during flicker stimulation ( $p < 0.0001$ ). Diclofenac significantly reduced the arteriolar contraction during isometric exercise ( $p = 0.005$ ) and significantly increased the flicker-induced dilatation of the venules ( $p = 0.03$ ). Nitroglycerine alone showed no effect on the diameters.

Conclusion: Diameter changes of retinal vessels during hypoxia are affected by inhibition of COX-products, while the effect of increased NO needs to be further clarified.

P01.10      Lisa Grønbaek Nielsen      DOES BMI MODIFY THE ASSOCIATIONS BETWEEN HbA<sub>1c</sub>, CARDIOVASCULAR EVENTS AND ALL-CAUSE MORTALITY AMONG PEOPLE WITH TYPE 2 DIABETES?

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Background: The associations between HbA<sub>1c</sub>, BMI, cardiovascular morbidity and all-cause mortality have previously been investigated among people with type 2 diabetes. Both U-shaped and linear associations have been found. The obesity paradox implies greater survival among people with some chronic diseases who are overweight or obese compared to normal weight individuals. Considering this, we aim to examine whether BMI among people type 2 diabetes modify the associations between HbA<sub>1c</sub> and 1) cardiovascular events and 2) all-cause mortality.

Method: This is a prospective cohort study including 1432 patients aged 40-69 with type 2 diabetes identified at baseline in 2001-2006 through the Danish arm of the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-detected Diabetes in Primary Care (ADDITION-DK). Baseline data were obtained by clinical examination, blood tests and questionnaires. Outcomes were cardiovascular events until 2010 and all-cause mortality until 2014 obtained from medical records and national registers. Based on BMI, three groups were formed. Hazard ratios for the associations between baseline HbA<sub>1c</sub>, cardiovascular events and all-cause mortality will be estimated in each group using Cox regression model. The results will be adjusted for age, gender, smoking status, alcohol consumption and physical activity.

Results: Preliminary results indicate that among people with type 2 diabetes, BMI is negatively associated with baseline age, smoking status, alcohol consumption and physical activity and positively associated with baseline triglyceride, antihypertensive medication and HbA<sub>1c</sub>. Full results

and conclusion will be presented at PhD Day 2015.

P02.01      Lars Bossen      THE EFFECT OF NON-SELECTIVE BETA-BLOCKERS ON MORTALITY IN CIRRHOTIC PATIENTS WITH OR WITHOUT REFRACTORY ASCITES

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Background: Liver cirrhosis increases the portal venous pressure, and this contributes to the development of esophageal varices and ascites. Non-selective  $\beta$ -blockers (NSBB) are the standard treatment to prevent bleeding from esophageal varices, but their use in patients with the most severe form of ascites has been questioned in recent studies. They showed that NSBBs increase mortality in patients with ascites that cannot be managed with diuretics ("refractory ascites"). Some have suggested that refractory ascites represents a threshold where NSBBs impairment of the cardiac function reaches a level associated with increased mortality. Therefore, a window-hypothesis suggests that NSBB should be discontinued when patients develop refractory ascites.

Aim: We want to investigate the effect of NSBB on mortality in cirrhotic patients with or without refractory ascites.

Methods: In 2006-2008, 1198 patients with cirrhosis and ascites were enrolled in three multicentre randomised double-blind studies comparing satoravaptan with placebo in reducing ascites. The investigators collected detailed information on a wide set of variables including NSBB use and refractory ascites. We will use these data to analyse the effect of NSBB on mortality in cirrhotic patients.

Results: We don't have any results yet, but we will use Kaplan-Meier estimates and a Cox model to analyse all-cause mortality. We will compare NSBB users to non-users in both patients with and without refractory ascites and adjust these results for cirrhosis severity and comorbidity.

Perspectives: We expect our results to help clinicians decide whether or not to avoid NSBB use in cirrhotic patients with refractory ascites.

P02.02      Anne Sofie Hansen      BLOOD DONATION AND RISK OF INFECTION

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Background: Throughout evolution, host and microorganism have struggled for iron during infection of the former. Studies indicate a higher risk of infection in patients with iron overload. Blood donation can cause iron depletion in regular blood donors, potentially protecting against infection.

Materials and methods: The project included 37,808 participants from The Danish Blood Donor Study, which was initiated March 1st, 2010. Participants fill out a questionnaire on health status, lifestyle and anthropometrics and blood samples are collected. Infections among participants have been identified as relevant ICD-10 codes in the National Patient Register and as relevant ATC-codes of antibiotics in the Danish Prescription Registry. We will assess the association between blood donation and subsequent risk of infection by estimating incidence rates of infection at various times after donation and we will compare the risk of infection after whole blood donations and apheresis in donors donating both.

Results: We hypothesize that blood donation decreases the risk of infection due to loss of iron.

Perspectives: Approximately 230,000 donors donate blood annually in Denmark. Thus, even a small association between donation and risk of infection could have an impact on a large number of donors, providing valuable information on the overall health risks and benefits of blood donation. If an association were to be found, this would have implications for our understanding of the role of iron in infection. If no association is found, the large size of the cohort would lead us to conclude that blood donation is not clinically relevant for the risk of infection.

P02.03	Anne Høy Seemann Vestergaard	END-OF-LIFE TRAJECTORIES OF CANCER VERSUS CHRONIC ILLNESSES: A NATIONWIDE STUDY
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Background: Life-extending treatment for some cancer types has advanced over the past years. These improvements are likely to have implications for trajectories at the end of life which may for some cancers begin to resemble trajectories of patients with non-malignant chronic illnesses with a slowly declining physical function over many years. However, detailed real life data on trajectories of cancer compared to non-malignant diseases is sparse.

**Aims:** To examine trajectories by studying monthly hospital admissions including intensive care unit (ICU) admissions within five years before death among patients dying from cancer, and to compare these trajectories with those of patients who died of chronic obstructive

pulmonary disease (COPD) or heart failure.

Method: Nationwide follow-up study based on linkage of national medical registries and clinical databases including all decedents in Denmark in 2010-2012 dying from cancer, COPD, or heart failure using the Danish Registry of Causes of Death.

Data on hospital admissions including ICU admissions have been obtained from the Danish National Registry of Patients, Danish Cancer Registry, Danish Registry for Chronic Obstructive Pulmonary Disease, and Danish Registry of Heart Failure.

Results: Monthly length of stays and hospitalization rates will be computed, plotted, and compared by regression analyses adjusted for covariates. Results will be stratified by cancer site and stage and by severity of chronic illness.

Conclusion: We expect this study to contribute to the understanding of trajectories of life-threatening illness and qualify the present view of different paths optimising palliative care in different types of trajectories.

P02.04      Camilla  
Cederbek  
Kjeldsen

#### REAL TIME URGE REGISTRATION WITH A SMARTPHONE APP AMONG PATIENTS WITH FECAL INCONTINENCE

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Background: Fecal incontinence (FI) is a distressing condition with a prevalence of 5 % among the older (>60 years) general population. Fecal incontinence can be either passive or with urge. It is established that fecal urge is an important predictor for the effect of the treatment sacral nerve stimulation and fecal urge is therefore a key symptom to be measured accurately. The current bowel habit diary is insufficient and lacks timeframe by which the degree of fecal urge is imprecisely measured.

Aim: To investigate and validate the use of a smartphone application (RETUR) as modern patient reported outcome and as a clinical tool in the field of FI.

Methods: The study is a population-based cohort study involving patients with idiopathic FI and a control group from the general population matched by age and gender. The participants register their fecal habits using both the RETUR App and the original paper diary during a 3 week follow up time. The primary endpoint is > 70% correct registration from > 70% of the study population.

Perspective: The use of innovative technology in the field of clinical medicine directs the Danish Health Care towards a more international competitive future. This study hopes to implement an accurate clinical tool that improves the course of treatment for patients with FI. To optimize the potential of distribution, the application is designed so that the backbone

of RETUR is well suitable to be used in other fields such as urology and gynecology.

P02.05	Anne-Sofie Greve Christensen	<p>THE EFFECT OF P2-RECEPTOR INHIBITION ON THE CYTOTOXIC EFFECT OF ALFA-HAEMOLYSIN FROM E.COLI - A MURINE SEPSIS MODEL</p> <p><i>A.S. Greve, M. Skals, H.A. Prætorius</i></p> <p>My institution (click to change me)</p> <p>Haemolytic bacterial toxins causes cell lysis by forming pores in plasma membranes. However, we demonstrated that -haemolysin (HlyA) secreted from E. coli, require extracellular ATP to cause cell lysis. This ATP is released directly through the HlyA pore and activates specific ligand-gated ion channels (P2X-receptors), which in turn is responsible for the lysis<sup>1</sup>. Interestingly, free plasma haemoglobin is associated with a poorer outcome of sepsis both in mice and in patients.</p> <p>Hypothesis: Inhibition of P2X receptors will improve the outcome of experimental induced sepsis with HlyA producing E. coli in a murine model.</p> <p>Methods: The project include to murine models:</p> <p>1) IV injection of HlyA producing E. coli in anaesthetised mice for determination of the role of P2X receptors on LD<sub>50</sub>.</p> <p>2) Peritoneal installation of HlyA-producing E. coli in mucin and haemoglobin for evaluation of the early septic events (24 h) and the effect of P2X receptor blockade.</p> <p>Results: To detect subtle haemolysis in blood from the septic mice, I screened optical density spectra of supernatant of erythrocytes incubated with HlyA. At 410 nm, lysis of 23,000 erythrocytes pr ml can be detected with accuracy, which corresponds to the sensitivity of haemoglobin ELISA assays. Moreover, I have tested 4 possible P2X<sub>7</sub>receptor blockers on human and murine erythrocytes, which to determine which will be included in this study. The most selective P2X<sub>7</sub>antagonist A839977 shows 35% reduction of HlyA-induced haemolysis.</p> <p>Conclusion: Based on the current data, I have selected a more generalised P2XR blocker and ready to start the experiments with the murine sepsis model.</p>
P02.06	Sissel Ravn	<p>THE INCIDENCE AND MORBIDITY OF INCISIONAL HERNIAS AFTER CYTOREDUCTIVE SURGERY WITH HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY: AN OBSERVATIONAL PROSPECTIVE COHORT STUDY</p> <p><i>S. Ravn, S. Harsløf, H. Thaysen, L. Iversen</i></p> <p>Department of Surgery (P), Aarhus University Hospital</p>

Background: Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is offered with curative intent to selected patients with peritoneal carcinomatosis from different origin. The Danish national CRS and HIPEC center has estimated favorable long-term survival results comparable with international studies. In spite of the documented increasing survival rates, the procedure is still extensive and the postoperative morbidity is substantial. Incisional hernia is a well-known complication following open abdominal surgery, and the risk after midline laparotomy has been reported to be 20%.

Primary objectives: To investigate the incidence of incisional hernias in a cohort of patients with peritoneal malignancy treated with CRS and HIPEC.

Secondary objectives: To investigate 1) the relationship between time after surgery and development of an incisional hernia, 2) the health-related Quality of Life (HRQoL) in patients undergoing CRS with HIPEC, and 3) whether incisional hernias have an impact on HRQoL.

Methods: An observational prospective cohort study based on a population of patients from Aarhus University Hospital with peritoneal carcinomatosis. Patients are scheduled for follow-up visits at 3, 6, 12, 18 and 24 months postoperatively. At each visit a clinical examination will be conducted and the patient will be asked to fill out three questionnaires regarding generic and cancer-specific HRQoL.

Perspectives: If there is a significantly increased incidence of incisional hernias following CRS with HIPEC, hopefully, we will be able to tell if this has a significant impact on QoL. If it is a substantial problem, this will open an opportunity to seek into future recommendations.

P02.07      Sissel Ravn  
                 Andersen      GASTROINTESTINAL MOTILITY AND SLEEP DISTURBANCES IN QUIESCENT CROHN'S DISEASE

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Objective: Approximately 40% of patients with quiescent Crohn's disease suffer from persisting gastrointestinal symptoms that negatively affect their quality of life. Sleep disturbance is another major complaint among this group of patients. Disrupted sleep with multiple arousals and a major part of the sleep being light (i.e. phase one) has been associated to disease activity in a number of immune-mediated diseases. We, therefore, aim to study the gastrointestinal motility patterns and disturbed sleep objectively to obtain a more accurate understanding of the etiology of the symptoms in the quiescent phases of the disease.

Methods: Our population will be 20 patients with quiescent Crohn's Disease recruited from the outpatient gastroenterologic clinic at Aarhus University Hospital. With a novel capsule system, 3D-transit, we are able to assess both total and regional transit times as well as nocturnal colonic motility patterns in a single ambulatory examination. The addition of polysomnography will



enable us to comprehensively study and quantify overall sleep quality and colonic motility in correlation to depth of sleep. A validated questionnaire will reveal the correlation between subjective and objective sleep disturbances and relate to cytokine levels measured in blood samples.

Results: Pending.

Conclusion: A large group of patients with quiescent Crohn's Disease suffers from gastrointestinal symptoms and sleep disturbances that cannot be attributed to active inflammation of the gut. We will investigate the gastrointestinal motility and the sleep quality of this group in detail to help avoid mistreatment and overtreatment of this group of patients.

P02.08      Kasper Grooss      CANCER DIAGNOSIS AND CHANGE OF GENERAL PRACTITIONER

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Background: Over the last decade, cancer has been the leading cause of death in Denmark. The GP plays a key role in diagnosing and following up on cancer patients. Due to unspecific symptoms, diagnosing cancer may be prolonged and dissatisfactory to some patients. Change of GP without change of address may be an expression of discontent with the received care and pose an issue for general practice; leading to a less optimal cancer trajectory with low support and continuity from general practice.

Aim: We aim to examine if cancer patients change GP more than non-cancer references; and if the change relates to socio-demographic factors or type of cancer.

Method: Using registry data, a population-based matched comparative study will be conducted by comparing a historical cohort of cancer patients to an age-, sex- and practice-matched cancer-free reference cohort. All first-time incident cancer cases aged 18 years or more from 2003-2012 will be included. Incidence density sampling will be used to randomly select ten references for each patient.

Analysis: Frequency of change of GP among cancer patients will be compared to non-cancer references and any modifying effects of socio-demographic factors or cancer types will be explored.

Perspectives: The study will present the first evidence on how often patients change GP in relation to a cancer diagnosis. Further, information will be gained on challenges regarding provision of support and continuity for patients in relation to diagnosis and treatment for cancer.

P02.09      Søren Viborg      LOWER GASTROINTESTINAL BLEEDING AND RISK OF GASTROINTESTINAL CANCER

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**Background:** Lower gastrointestinal (GI) bleeding is a well-known first symptom of colorectal cancer (CRC). However, whether it is a marker of other GI cancers, and how long a potential excess cancer risk persist in patients with incident bleeding diagnosed in-hospital have been sparsely investigated.

**Methods:** This nationwide cohort study examined the risk of various types of GI cancer in patients with lower GI bleeding. We used Danish medical registries to identify all patients with a first-time hospital diagnosis of lower GI bleeding (1995-2011) and followed them up to 10 years for subsequent GI cancer diagnoses. We computed absolute risks of cancer, treating death as competing risk, and standardized incidence ratios (SIRs), by comparing observed cancer cases with national general population cancer incidence rates.

**Results:** Among 60,093 patients (49% men) with lower GI bleeding, we observed 2,918 GI cancers during complete follow-up, corresponding to an overall SIR of 3.63 (95% confidence interval (CI): 3.50-3.77). During the first year of follow-up, patients had an overall absolute GI cancer risk of 3.6%, corresponding to a SIR of 16.1 (95% CI: 15.4-16.8), mainly due to an excess of CRCs, but all GI cancers were diagnosed more frequently than expected. After 5 or more years, the overall cancer risk declined to close to unity, but of note, an increased risk of liver and pancreatic cancer persisted, whereas there was a reduced risk of distal colon and rectal cancer.

**Conclusions:** Lower GI bleeding is a strong clinical marker of prevalent GI cancer, particularly CRC, but it also predicts an increased risk of liver and pancreatic cancer even beyond 5 years of follow-up.

P02.10 Jens Tilma

TREATMENT INJURIES IN DANISH PUBLIC HOSPITALS 2006-2012

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**Background:** Treatment injuries are responsible for substantial mortality, morbidity and financial costs. Examining data from closed claims is a potential effective way to identify pitfalls in patient safety and design interventions to reduce injuries.

**Aim:** We aimed to determine the incidence of accepted treatment injuries in Danish public hospitals from 2006 through 2012 and to identify independent predictors of severe treatment injuries amongst patient and system characteristics.

**Methods:** We performed a nationwide, historical observational study on data from the Danish Patient Compensation Association, which receives all compensation claims from health care in Denmark. Included: All approved

and compensated closed claims of treatment injuries occurring in 2006-2012. Information on health care activity was obtained from the Danish National Registry of Patients. Incidence rates were determined as treatment injuries per year and per admissions per year, respectively. We used a multivariable logistic regression model to assess the association between potential predictors and severe treatment injuries.

Results (preliminary): We identified 10,959 approved claims for treatment injuries occurring in 2006-2012. The total payout was 400 million USD. Severe permanent injury or death occurred in 10.4% (95%CI: 9.9;11.0) of the cases. The mean incidence rates were 27.85 (SD=4.75) injuries per 100,000 inhabitants per year and 1.24 (SD=0.24) injuries per 1000 admissions per year. Potential predictors of severe injury under investigation include age, gender, comorbidity, medical specialty, and region/hospital. (Data will follow).

Conclusion: Awaiting further data.

P03.01 Carina Madsen MATERNAL COFFEE CONSUMPTION DURING PREGNANCY AND RISK OF CHILDHOOD ACUTE LEUKEMIA

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Background: Acute leukemia (AL) is the commonest childhood cancer, and only little is known about the etiology. Because of the young age at diagnosis a causal window occurring in the pre- or perinatal period has been suggested. Coffee intake is a potential causal candidate. The best known compound in coffee is caffeine. Evidence indicates that caffeine might exhibit a carcinogenic effect triggering chromosomal changes that may induce childhood AL. The association between prenatal caffeine exposure and risk of childhood AL has been examined in a few case control studies showing an association, which may be due to bias from retrospectively collected information of prenatal coffee exposure.

Aim: To investigate the association between coffee intake during pregnancy and childhood AL, using three Danish population based birth cohorts. To our knowledge, this will be the first follow-up study to analyze this association.

Method: Data will be obtained from the Danish National Birth Cohort, the Aarhus Birth Cohort, and the Healthy Habits for Two Cohort. Main exposure of interest is antenatal coffee intake. This information is collected during pregnancy in all three cohorts. Outcome is AL diagnosed in the offspring before age of 16 years. Information on AL will be obtained from the Danish National Patient Register. Cox-regression analysis will be performed. Possible confounders will be chosen a priori based on covariates known in literature to be potential risk factors of AL.

Perspective: A positive association will present a potential preventable

causal component in the causal field leading to childhood AL. Also, it will affect the current guidelines on prenatal coffee intake.

P03.02      Sham Husain      MRI AND PET/CT SCAN USED IN STAGING OF CERVICAL CANCER BEFORE SURGERY

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Introduction: The prognosis in women with cervical cancer (CC) not only depends on the tumor size and expansion, but also on a variety of additional findings as vascular invasion, infiltration of the tumor, metastasis to local lymph nodes and distant metastases. According to the international recommendations by the Federation of Gynaecology and Obstetrics (FIGO), staging is executed during gynecological examination under general anesthesia, and treatment is planned suitably. This method is cheap and can, therefore, be used globally although it does not take lymph node metastases into account, and these are consequently discovered during surgery. In case of metastasis, radiotherapy or chemotherapy is needed, and surgery is terminated. Since 2009, PET/CT and MRI have become additional diagnostic tools to the gynecological examination in the staging of CC according to FIGO. PET/CT and MRI are valuable tools in respectively detecting lymph node metastases and size, expansion and infiltration of the tumor. The aim is to prevent any unnecessary surgical procedures if radio- and chemotherapy is needed.

Perspective: We wish to clarify if MRI and PET/CT have had a positive impact on staging and treatment of women with diagnosed CC by visualizing the cancer better for more correct staging and by reducing the number of women undergoing surgery and adjuvant radiotherapy and chemotherapy.

Method: We carry out a retrospective longitudinal study on women who have been histopathologically diagnosed with CC and referred to Aarhus University Hospital for staging of CC from the year 2009 and 2014. The expected number of patients is 300.

P03.03      Anna Hartmann Schmidt      LOCAL RECURRENCE AND LATE COMPLICATIONS AFTER SIMPLE RESECTION OF RESIDUAL METASTASIS AFTER CHEMOTHERAPY IN NON-SEMINOMATOUS TESTICULAR CANCER

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Introduction: About half of the patients who undergo induction chemotherapy for disseminated testicular non-seminomatous germ cell tumour (NSGCT) have significant residual retroperitoneal disease. The residual tumours (RT) consist of either necrosis, teratoma or active malignant cells.

Danish guidelines recommend removal of RT by a simple resection while a full template lymphnode dissection (TLND) is performed at other centres.

**Aim:** We aim to investigate the outcome and complications following the operation for RT performed in Aarhus, Denmark. Furthermore, we will investigate the quality of life after surgery compared to a relevant control group.

**Patients and methods:** In the period 1993-2013, 200 patients received induction chemotherapy and post chemotherapy surgery owing to disseminated NSGCT at Aarhus University Hospital. The control group consists of patients having disseminated NSGCT without RT after chemotherapy. They match the patients in age, chemotherapy and year of treatment. A questionnaire regarding quality of life (EORTC QLQ--C30) and 12 questions related to specific late complications have been distributed to both the patients and the control group. Hospital records and questionnaires are reviewed. Data regarding disease, surgery, recurrence and complications are collected into a database.

**Hypothesis and perspective:** We hypothesize that NSGCT patients receiving surgery targeted to RT have fewer complications and an equal risk of recurrence compared to patients receiving TLND. The results may affect the future strategy of surgery used to treat NSGCT patients harbouring residual retroperitoneal disease.

P03.04      Anne Møller      PROSTANOID-INDUCED CONTRACTION OF HUMAN PLACENTAL STEM VILLI VEINS IS MODULATED BY A PERIVASCULAR-DERIVED DILATION FACTOR

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**Objective:** Sufficient placental blood flow is crucial for normal pregnancy outcome and partly determined by the vascular resistance, including the contraction and dilatation of the stem villous veins (SVV). Prostaglandin F<sub>2α</sub>(PGF<sub>2α</sub>) is considered to be an important contractile factor and nitric oxide (NO) a potent vasodilator. Placental vessels are covered by a perivascular tissue (PVT) and, in contrast to other vascular beds, the SVV transport the oxygenated and nutrient-rich blood. However, the interaction between SVV, PTV and NO has not been investigated. We hypothesized that the presence of PVT modifies the sensitivity and maximum contractility to PGF<sub>2α</sub> in SVV and that this effect is influenced by the NOS system.

**Method:** SVV from uncomplicated pregnancies were dissected under a stereo microscope. One half of the vessel was left unprocessed while the PVT was removed from the other half. Then mounted individually on a wire myograph (DMT) and investigated in terms of contractility and sensitivity to cumulative doses of PGF<sub>2α</sub> (10<sup>-9</sup> to 3×10<sup>-4</sup>M) prior to and after incubation with the NO-synthase inhibitor L-NNA (10<sup>-4</sup>M). Contractility was measured

as the maximal force developed,  $E_{\max}$ , and sensitivity as  $pD_2$ .

Results: The PVT significantly suppresses  $E_{\max}$  to  $PGF_{2\alpha}$  in SVV and the effect is influenced by the NOS system localized in the PVT. No significant differences were seen for  $pD_2$ .

Conclusion: We see a tendency that the PVT surrounding SVV suppresses maximal force development; this effect is partly blocked by L-NNA. No equivalent changes were seen for sensitivity. Further experiments are necessary in order to determine how this perivascular tissue exerts its effect.

P03.05      Ulla Juul      LAPAROSCOPIC HYSTERECTOMY - A RANDOMIZED CONTROLLED STUDY  
Christiansen      ON OUTPATIENT VERSUS INPATIENT REGIMEN.

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Objective: We wish to examine patient satisfaction, physical activity, length of actual sick-leave and the economic impact for women discharged 6 to 8 hours after laparoscopic hysterectomy.

Methods: A randomized controlled study on outpatient versus inpatient laparoscopic hysterectomy (LH). The study takes place at the Department of Gynecology, Regionshospitalet Herning. Our sample size on 90 participants in each group consists of women from this area, less than 56 years old and scheduled for LH on benign indication. All the women will follow the same procedures on the day of surgery till the evening where the women randomized to the outpatient group are leaving the ward. The inpatient group will remain in the ward to the next morning. All women are equipped with a log and a pedometer. The women are expected to fill in the log preoperatively and 6 times postoperatively.

Hypothesis: This study will test the primary hypothesis that more than 20% of patients are less satisfied/dissatisfied with the length of hospital stay after outpatient LH, compared with 5% of patients after conventional inpatient LH. Secondary hypotheses are: Incidence and pattern of complications are similar for in- and outpatient LH; similar physical activity measured by a pedometer for in- and outpatient LH; similar time to return to work will be found for in- and outpatient LH; sick leave after LH shows variations according to local status and socioeconomic status.

Perspectives: An RCT of LH performed as an outpatient procedure compared with current inpatient standard will provide a firm platform for future planning of routine treatment of patients with need of a benign hysterectomy.

P03.06      Thor Haahr      DOES BACTERIAL VAGINOSIS AFFECT FEMALE FECUNDITY?

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Background: Bacterial Vaginosis (BV) is a common polymicrobial infection among women in the reproductive age. In the fertility population, a recent meta-analysis has shown the prevalence of BV to be 19%. This prevalence is significantly higher than in the general fertile population, thus suggesting a causal link between poor female fecundity and BV. It is evident that *Gardnerella Vaginalis* is capable of establishing an ascending infection to the endometrium. We speculate that a *Gardnerella Vaginalis* infection present in the vagina might ascend to the endometrium creating an inflamed endometrium that rejects the embryo during the implantation process.

Objective: The primary objective is to address whether or not BV affects the implantation rate. Secondly, we investigate a molecular defined microbial community dominated by *Gardnerella Vaginalis* and its association to IVF outcome.

Methods: We included 200 women from two fertility clinics in Denmark. BV diagnosis was performed independently by two medical laboratory technologists and if discordance a third and final diagnostic view was performed by a microbiologist. PCR analyses are currently being performed at Statens Serum Institut, Denmark. Briefly bacterial DNA was extracted and 16srRNA probes were mixed before quantitative realtime PCR analysis.

Preliminary results: 24.3 % (17/70) had BV among female fertility patients. The preliminary implantation rate is lower among BV positives (13%) than among BV negative controls (39%).

Discussion: We emphasize the small sample size in our preliminary results. However, our findings suggest a new frontier in fertility treatment with screening and sub-sequent treatment for BV.

P03.07      Saga Elise      MATERNAL PRE-PREGNANCY BMI AND REPRODUCTIVE HEALTH OF  
                 Mariansdatter      DAUGHTERS IN YOUNG ADULTHOOD

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Background: Fat is a hormonally active tissue, and increasing body mass index (BMI) positively correlates with plasma concentrations of certain endocrine disrupting compounds. Few studies have examined the association between maternal pre-pregnancy BMI and age of menarche (AOM) in daughters, while the impact on later markers of female

reproductive health has not yet been studied.

Objective: To examine the possible association between maternal pre-pregnancy BMI and AOM, ovarian follicle count and serum levels of reproductive hormones in 19-21-year-old daughters.

Methods: In a Danish pregnancy cohort established in 1988-1989, maternal pre-pregnancy BMI was obtained at interviews during pregnancy. In 2008, AOM was obtained through a self-administered questionnaire for 365 daughters, and 267 daughters participated in a subsequent clinical examination. Daughters were divided into three exposure groups according to maternal BMI tertiles [lower ( $\leq 20.0$ ), middle (20.0-21.9, reference), higher ( $\geq 22.0$ )]. Data were analyzed using multiple linear regression.

Results: Daughters of mothers in the highest BMI tertile had an adjusted 4.1 [0.3; 8.0] months earlier AOM compared to the reference group. For the same exposure group, those that were non-users of oral contraceptives (OC's) showed a tendency towards lower follicle counts and serum levels of estradiol, free estradiol and DHEAS, and a higher free androgen index/free estradiol ratio.

Conclusion: Higher maternal BMI was associated with earlier AOM. A possible impact of higher maternal pre-pregnancy BMI on follicle counts and hormone levels in non-users of OC's was indicated, but the analyses were limited by small sample sizes.

P03.08      Lotte  
Kaasgaard  
Jakobsen

#### UROGENITAL RECONSTRUCTIVE SURGERY

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Background: Congenital obstruction of the lower urinary tract causes voiding disabilities, renal failure and chronic bladder changes. Children with such malformations often require extensive treatment, and will experience side effects and not always satisfactory results.

Aim: To develop an animal model of congenital infravesical obstruction, and utilise it to characterise changes caused by obstruction and effects of different treatment options.

Material and methods: Four groups of swine will be investigated. Urethral obstruction will be created surgically in groups 2-4. After 4 weeks continuous unloading will be performed by vesicostomy in group 3, and intermittent unloading by urethrostomy in group 4. Group 2 will not be unloaded and serve as continuously obstructed controls, whilst group 1 serves as sham-operated, non-obstructed controls. Urodynamic assessment will be performed and samples of urine, blood and bladder tissue will be collected.

To supplement the experimental studies we will evaluate patients with



posterior urethral valves, and compare the effects of obstruction seen in these patients with the effects observed in the animal model.

Bladder tissue from fetal pigs will be investigated, comparing the properties of the fetal bladder to those of the bladder from young pigs used in the animal model.

Results: By further characterising the effect of congenital obstruction, regarding urodynamic properties of the bladder and structural changes in the bladder tissue and comparing the results after relief of obstruction by continuous or intermittent means, we hope to make it easier to choose which treatment to offer the patients. By establishing a solid animal model of congenital infravesical obstruction, we expect to make way for development of better treatments of a rare, but serious condition.

P04.01      Jonas Jensen      INFLUENCE OF ORGANIC CATION TRANSPORTER 1 AND 2 IN PHARMACOKINETIC OF METFORMIN

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Objective: Today, metformin is considered as a cornerstone in treatment of type 2 diabetes and is globally prescribed to more than 100 mio. Patients annually. However, the drug is challenged by a large inter-individual therapeutic effect which in part can be explained by pharmacokinetic factors. Because of a hydrophilic nature, cellular uptake of metformin is depended on cation transporters. Organic Cation Transporter 1 and 2 (OCT1 and 2) seem to take part in hepatic uptake and renal elimination of metformin, respectively. To investigate the influence of these two transporters in specific tissue uptake of metformin, we used PET-scans with C11-labeled metformin in an OCT1/2-dobbel-knockout mouse model.

Methods: 7 wild type and 4 OCT1/2-dobbel-knockout mice underwent 60 min. dynamic PET-scan with C11 metformin followed by anatomical MRI using Mediso nanoScan PET/MR. Mice were anesthetized with 2% isoflurane whereafter C11 metformin ( $5.7 \pm 2.8$  mBq) was administered as a single bolus into the tail vein. Specific tissue uptake was quantified using liver and kidneys as regions of interest.

Results: Relative liver uptake of C11 metformin was 2-fold lower and relative peak uptake in the kidneys was 4-fold lower in OCT1/2 knockout mice when compared to wild type.

Conclusion: Specific tissue uptake of C11 metformin is markedly affected by absence of OCT1 and 2. Perspectives of this novel PET tracer include in vivo studying of drug-drug interactions, kidney imaging, influence of transporter mutations, etc., which can add knowledge in relation to treatment optimizing and personalized medicine.

- P04.02 Dina Michelle Baarts Pedersen THE ROLE OF MICRORNAS IN OBSTRUCTIVE NEPHROPATHY  
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Background: The mechanism behind obstructive nephropathy and how inflammation and fibrosis is regulated is incomplete. MicroRNAs (miRNAs) are short non-coding RNA molecules that modulate physiological and pathological processes by inhibiting target gene expression via blockade of protein translation or by inducing mRNA degradation. We hypothesized that specific miRNA play a role in the progression of renal inflammation and fibrosis in response to obstructive nephropathy.

Aim: To use both in vivo and in vitro studies to examine the effects of different miRNAs on the progression of inflammation and fibrosis.

Methods: In the in vitro studies, we use macrophage RAW cells transfected with different miRNAs and exposed to LPS treatment. We then study the regulation of inflammation and fibrosis markers, to test which is the best miRNA for our in vivo studies. In vivo mice were subjected to unilateral ureteral obstruction (UUO) for 3 and/or 7 days and administrated with miRNA using a nanoparticle system. In vivo optical imaging was used for nanoparticle tracking and the effect of the miRNA was studied for the progression of inflammation and fibrosis.

Results: So far, we have performed in vivo biodistribution studies demonstrating that chitosan and folic acid nanoparticles injected IP are accumulated in the macrophages in the obstructed kidney. IV injection of liposome nanoparticles did not accumulate in the kidneys. These data suggest that IP injection using chitosan or folic acid is the best choice for delivering our miRNA to our in vivo model.

Perspectives: We hope to create a better understanding of new treatment options for patients with obstructive nephropathy.

- P04.03 Stine Høgsholt HEALTH CONDITION IN SURVIVORS OF WILMS TUMOR: A NORDIC POPULATION-BASED COHORT STUDY

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Background: With modern therapy for Wilms tumor, nine out of ten patients can expect to become long-term survivors. However, late onset health consequences are a major concern. The objective of this study is to investigate the spectrum and frequency for late sequelae in survivors of Wilms tumor.

Methods: This study is part of the inter-Nordic collaboration Adult Life after

Childhood Cancer in Scandinavia (ALiCCS). From the cancer registries in the five Nordic countries, we identified 1316 one-year survivors of Wilms tumor diagnosed <20 years of age. For each patient with Wilms tumor, we randomly sampled five comparison individuals from the general population. We followed the study subjects for hospitalizations in the national hospital registries. The rate of hospitalization for diseases in different organ systems among the Wilms tumor survivors was compared to an expected rate based on the comparisons.

Results: Survivors of renal tumors are at increased risk of being hospitalized for renal disorders (RR 3.9; 95% CI 3.2-4.7), cardiovascular disease (RR 2.8; 95% CI 2.3-3.4), gastrointestinal disease (RR 1.6; 95% CI 1.6-1.7) or endocrine disorders (RR 3.7; 95% CI 3.1-4.5). Among specific disease entities some of the highest risks were seen for chronic renal disease (RR 12.6; 95% CI 8.9-17.7) and vascular disease of the intestines (RR 24; 95% CI 8.5 to 70).

Conclusions: Survivors of Wilms tumor had an increased risk of a wide range of diseases with the highest risks of disease in organs with close anatomical relation to the kidney. Further studies should examine the impact of cancer therapy related risk factors such as irradiation and chemotherapy.

P04.04      Jeppe Steen      SODIUM/BICARBONATE-COTRANSPORTER SLC4A7 MEDIATES THE  
Olsen      INCREASED BASOLATERAL BICARBONATE UPTAKE IN RENAL THICK  
ASCENDING LIMBS DURING METABOLIC ACIDOSIS

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Background: The  $\text{Na}^+/\text{HCO}_3^-$ -cotransporter NBCn1 (Slc4a7) is located in basolateral membranes of renal thick ascending limbs (TAL) and its expression increases during metabolic acidosis (MAC). It has been hypothesized that NBCn1 promotes the medullary  $\text{NH}_4^+$ -gradient that favors acid excretion.

Objectives: We will determine if NBCn1 contributes to basolateral net acid extrusion in TAL and if it is functionally upregulated during MAC.

Methods: We measured intracellular pH ( $\text{pH}_i$ ) in isolated perfused TAL from WT and NBCn1 KO mice. To induce MAC, mice were loaded with 0.196 M  $\text{NH}_4\text{Cl}$  in the drinking water for 4 days.

Results: RT-PCR and immunoblotting demonstrated expression of NBCn1 in TAL of WT but not NBCn1 KO mice. RT-PCR also revealed expression of other SLC4  $\text{HCO}_3^-$  transporters in TAL. These include NBCe1, NDCBE, AE4 and BTR4. Following an acute intracellular acid load, all mice showed  $\text{pH}_i$  recovery dependent on  $\text{Na}^+/\text{HCO}_3^-$ -cotransport. In untreated mice,  $\text{pH}_i$  recovery rate was not different between WT and NBCn1 KO mice.  $\text{NH}_4^+$  loaded WT mice showed a 3-fold increase in  $\text{pH}_i$  recovery rate compared to untreated animals, while the NBCn1 KO mice showed only a

small increase.

Conclusion: In control mice, NBCn1 does not contribute to net acid extrusion in TAL. However, under MAC, NBCn1 is responsible for the 3-fold increase in pH<sub>i</sub> recovery rate. Other SLC4 transporters are expressed in TAL and likely mediate the Na<sup>+</sup>,HCO<sub>3</sub><sup>-</sup> co transport under basal conditions. We propose that NBCn1 is important for facilitating net acid extrusion under MAC.

- P04.05     Silje Jørgensen   EXPANDING THE SPECTRUM OF GENETIC VARIATION CAUSING FAMILIAL  
                 Hovden            HYPOCALCIURIC HYPERCALCEMIA AND AUTOSOMAL DOMINANT  
                            HYPOCALCEMIA

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Familiar Hypocalciuric Hypercalcemia (FHH) is an autosomal dominantly inherited disorder characterized by hyperparathyroid hypercalcemia, predominantly without symptoms. The condition is often caused by gain-of-function mutations in the gene encoding the calcium sensing receptor (CASR). Whereas treatment is needless in FHH, primary hyperparathyroidism, a disease characterized by very similar biochemical features, requires surgery of the parathyroid glands to be controlled and cured. Distinguishing the two conditions is a challenge - only 65% of the suspected cases have a FHH-associated CASR-variant. Consequently, the risk of misdiagnosis and unfruitful neck exploration is high, and an estimated 23% of failed parathyroidectomies in Denmark are due to misdiagnosis.

Recently, genetic variants in two candidate genes were identified: AP2S1 and GNA11, of which 20% and 10 % respectively, were found to be associated with hypercalcemia in CASR-negative patients. GNA11 is also associated with autosomal dominant hypocalcemia (ADH), in more than 25% of unexplained cases of idiopathic hypocalcemia.

We hypothesize that variations in AP2S1 and GNA11 are the cause of FHH and ADH in Danish patients with a previously unexplained persistent hyper- or hypocalcemia. So far, we have established the molecular genetic analysis based on PCR and DNA sequencing, and have optimized the protocols - next step is analyzing patient-DNA.

This study aims to expand the spectrum of known genetic variation in FHH and ADH, and thereby improve the diagnostic approach to these patients. We expect to implement the analysis in the routine diagnostic of abnormalities in the calcium metabolism.

- P04.06     Samuel Levi     P2X RECEPTOR-MEDIATED INHIBITION OF NACL ABSORPTION IN THE  
                 Clement

Svendsen

## THICK ASCENDING LIMB: NO EVIDENCE FOR NO

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Background: Our group discovered that basolateral (bl.) P2X receptors acutely and markedly reduce NaCl absorption in mouse medullary thick ascending limb (mTAL). Others propose a mechanism of P2X receptor-mediated NO synthesis leading to NKCC2 inhibition. P2X receptor stimulation causes an increase in cytosolic  $\text{Ca}^{2+}$  and therefore this could be proximal to the generation of NO.

Objective: Here we tested if blocking NO synthesis or removal of extracellular  $\text{Ca}^{2+}$  inhibits the ATP-mediated (P2X) transport inhibition.

Methods: In this study we used isolated, perfused mTALs from mice to electrically measure  $\text{Na}^+$  absorption. By microelectrodes we determined the transepithelial voltage ( $V_{te}$ ) and the transepithelial resistance ( $R_{te}$ ) and via these the transepithelial  $\text{Na}^+$  absorption (equivalent short circuit current,  $I_{sc}$ ).

Results: We confirm that bl. ATP (100  $\mu\text{M}$ ) induced a marked, acute and reversible inhibition of  $\text{Na}^+$  absorption ( $28\% \pm 6\%$ ,  $n=6$ ). In the presence of the NO synthase blocker L-NAME (100  $\mu\text{M}$ , with 3 min preincubation) the ATP effect remained unaffected ( $23\% \pm 9\%$ ,  $n=6$ ). Also the removal of extracellular  $\text{Ca}^{2+}$  (100 nM, 2 min preincubation) had no effect on the ATP-induced transport inhibition ( $[\text{Ca}^{2+}]=100\text{nM}$ :  $21\% \pm 6\%$ ,  $n=5$ ,  $[\text{Ca}^{2+}]=1\mu\text{M}$ :  $24\% \pm 4\%$ ,  $n=6$ ).

Conclusion: We find no evidence for NO being involved in the signaling pathway for ATP-mediated transport inhibition. Similarly,  $\text{Ca}^{2+}$  signaling appears not involved in P2X receptor-mediated inhibition of NaCl absorption.

P04.07

Lea Lykke  
Braskhøj  
Lauridsen

## PUBERTAL DEVELOPMENT AND SEMEN QUALITY AND REPRODUCTIVE HORMONES IN YOUNG ADULT LIFE

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Background: Several studies have stated that the semen quality is at a critically low level, where it might affect the ability to conceive a child. Factors, that might affect this, are essential to identify, thus enabling correct treatment and understanding the sub-fertile couple.

Abnormal age at the onset of puberty is a risk factor for several health related issues in adult life, e.g. prostate cancer and testicular cancer. The possible association between age at pubertal development and male reproductive health in adult life is still unknown. We hypothesize that a delayed puberty is associated with a lower semen quality.

Methods: In 2005-06 a cohort of 347 Danish men enrolled in the 'Healthy Habits for two' cohort (18-21 years of age) provided self-reported,

retrospective data on indicators of pubertal development (age at first nocturnal emission, voice break and pubic hair). All 347 men delivered semen and blood sample. We will study the association between age at pubertal development and semen quality and reproductive hormones using multivariate logistic regression. Possible confounders will be identified using directed acyclic graphs (DAGs), and the results will be adjusted for potential confounding factors. Multiple imputations will be used to address any missing data problem.

Conclusion: It is important to identify possible factors affecting the male fecundity. This study will bring new information to this rather unexplored subject.

P04.08      Rahul Prabha      ENGINEERED BONE FOR OSSEOUS RESTORATION

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Background: Critical sized osseous defects caused by surgical interventions, osteotomies and distraction osteogenesis continues to be a challenge, requires bone grafting to restore form and function. Limitations of autologous bone grafting, like inadequate supply and donor site morbidity, have led to the development of alternatives like bone tissue engineering. The aim of this PhD project is to develop a clinical relevant protocol combining the classic techniques applied in the healing of bone defects in the craniofacial region with Human adult dental pulp stem cells (DPSCs) and scaffold based tissue engineering therapy in order to achieve enhanced bone regeneration. In this study DPSCs are also compared with Human bone marrow mesenchymal stem cells (BMSCs), which serve as the control.

Material and methods: Three scaffolds, namely Bioceramic granules, Electrospun membrane, and Injectable hydrogel, of distinct clinical application are used in this study. The study involves in vitro and in vivo scaffold characterization for osteogenic differentiation of DPSCs and BMSCs. The constructs would further be tested for efficient closure of critical sized bone defects in immunocompromised animal models.

Results: The chemical characterization of the Electrospun scaffolds confirmed the hypothesized hydrophilic nature and bioactive properties. In vitro experiments on the Electrospun membrane scaffold showed cell attachment, viability, proliferation, osteogenic differentiation and mineralization with both cell lines, DPSCs and BMSCs. The results from in vivo implantation of Electrospun scaffold in the critical sized calvarial defect indicated osteoconductivity and vascular in growth.

P04.09      Marie Bodilsen      RENAL BIOMARKERS AFTER DECEASED DONOR KIDNEY TRANSPLANTATION

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Background: Delayed graft function (DGF) is a common complication in deceased donor kidney transplantation. It is associated with poorer long-term graft function and survival and possibly a higher incidence of rejection. Validation of biomarkers for early detection of kidney graft dysfunction and for prediction of DGF and outcome would facilitate optimal clinical management after transplantation. Urinary and plasma biomarkers associate with ischemia-reperfusion injury and kidney transplantation. This study evaluates the association between early graft function and changes in NGAL, L-FABP, Cystatin C, and YKL-40 following deceased donor transplantation.

Materials and methods: Blood and urine samples are collected from 200 deceased donor kidney transplant recipients before, during, and after transplantation. Patients are included as part of a randomized, controlled, multicentre, clinical trial. Biomarkers will be analysed using ELISA and automated assays. Changes and variations in each biomarker will be examined and correlated with kidney function defined by changes in P-creatinine and GFR. The sensitivity and specificity of the biomarkers to predict DGF will be examined.

Results: We hypothesize that individual biomarkers and/or a combination of these will predict graft function, including DGF, after deceased donor transplantation. Analyses of the time dependent changes in each biomarker will identify the optimal time for sampling.

Conclusion: The study will provide additional information on the utility and diagnostic relevance of biomarkers in the evaluation of early graft function. This could facilitate early intervention to minimize the complications associated with DGF.

P04.10 Lise Sofie Bislev **PHYSIOLOGIC INTERACTIONS BETWEEN THE ADRENAL AND THE PARATHYROID GLANDS DESCRIBED BY CONTROLLED CLINICAL TRIALS - A DESCRIPTION OF A PHD PROJECT**

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Background: Increasing evidence suggests an association between parathyroid hormone (PTH) and aldosterone but so far, the association has not been studied in patients with secondary hyperparathyroidism. The possible correlation is interesting because it contributes to clarify a well-known association between conditions with hyperparathyroidism (osteoporosis, diseases in the parathyroid glands, vitamin D deficiency and renal failure) and cardiovascular disease (CVD).

Aim: To make a description of the association between PTH and aldosterone in patients with secondary hyperparathyroidism.

Hypothesis one: Normalization of vitamin D storages in patients with secondary hyperparathyroidism due to vitamin D deficiency: a) reduces plasma aldosterone, b) decreases the risk of CVD estimated by surrogate parameters measured by tonometry, c) increases bone mineral density and muscle strength and function, d) increases quality of life.

Hypothesis two: Inhibition of the renin-angiotensin-aldosterone system (RAAS) reduces the severity of secondary hyperparathyroidism in patients with vitamin D deficiency.

Methods: A randomized controlled double-blind study including 80 postmenopausal women (60-80 years) with secondary hyperparathyroidism. During 12 weeks in the winter, the women will receive a supplement of Vitamin D3 (cholecalciferol) 70 µg or placebo. Furthermore, the women are randomized to an angiotensin 2 receptor blocker (Valsartan, 80 mg per day) or placebo during the two first weeks of the study.

P05.01      Kris Chadwick    BONE MARROW ASPIRATE FOR CARTILAGE REPAIR  
                 Hede

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Introduction: Repair of focal articular cartilage defects is challenging and failure to regenerate the cartilage tissue leads to pain and disability and may cause early development of osteoarthritis. Currently, the best treatment available is autologous chondrocyte implantation (ACI). This treatment, however, has several disadvantages such as two surgeries and high costs. Therefore, there is great interest in developing new strategies for cartilage repair. The use of bone marrow aspirate concentrate (BMAC) as the cell source for cartilage repair has yielded some early promise. This method has the advantage of being a one-step procedure, reducing costs compared to ACI and related treatments and still has the benefits of the transplanted cells being autologous.

Aim: The aim of this study is to investigate the chondrogenic response of BMAC in vitro. We hypothesize that the chondrogenic response of BMAC is comparable to chondrocytes established from biopsies.

Methods: Mononuclear cells from bone marrow aspirate from healthy donors will be isolated through the use of Ficoll-Hypaque solution and centrifugation. These will be seeded on two types of three-dimensional scaffolds, as will autologous chondrocytes obtained from donors undergoing anterior cruciate ligament reconstruction. The chondrogenic response of the two cell types will be compared through quantitative gene expression and histology.

Perspectives: The study will provide necessary background data for



cartilage repair with BMAC as a one-step procedure. Based on the results obtained in this study we aim to apply for approval to continue in clinical phase I trials.

P05.02 Iben Jensen THE NATRIURETIC RESPONSE TO ACUTE POTASSIUM INTAKE

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Diets rich in  $K^+$  are associated with unexplained protection against hypertension. Acute  $K^+$  intake induces rapid natriuresis and kaliuresis in mammals. This is linked to marked dephosphorylation of renal  $Na^+/Cl^-$  cotransporters (NCC). Reduced activity of NCC increases  $Na^+$  delivery to the collecting ducts. This is hypothesized to increase ENaC-dependent electrogenic driving force for  $K^+$  secretion, allowing elimination of an acute  $K^+$  load.

We studied  $K^+$  and  $Na^+$  excretion in mice adapted to either preserve or promote  $Na^+$  loss. Mice were fed low (0.03%), control (0.2 %) or high (2%)  $Na^+$  diet for 25 days. Once a week, mice received gavage of either  $K^+$  or vehicle. Mice were placed in metabolic cages and urine was collected real-time. ENaC-dependence of kaliuresis was assessed by benzamil injections prior to gavage in a series of additional experiments.

Plasma aldosterone and cleavage-products of ENaC were inversely related to dietary  $Na^+$  content.  $K^+$  excretion rate was reduced in animals on high  $Na^+$  diet compared to the other groups. In all dietary groups, acute  $K^+$  -load induced natriuresis. However maximal  $Na^+$  excretion rate was reduced ~80% and increased ~15% in the  $Na^+$ -restricted and -loaded mice, respectively. Benzamil injection prior to  $K^+$  loading increased natriuresis and decreased kaliuresis. Importantly benzamil abolished all differences in kaliuresis and natriuresis between the groups.

Data suggest that acute  $K^+$ -induced kaliuresis is completely ENaC-dependent. Acute kaliuresis is associated with natriuresis, even during  $Na^+$  restriction. Furthermore, the ability to excrete  $K^+$  on high  $Na^+$  diet, resulting in low ENaC activity, is attenuated.

P05.03 Henrik Jonathan Münch THE ASSOCIATION BETWEEN METAL ALLERGY, TOTAL KNEE ARTHROPLASTY AND REVISION

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Background and purpose: It is unclear whether delayed type hypersensitivity reactions against implanted metals play a role in the etiopathogenesis of malfunctioning total knee arthroplasties. We, therefore, evaluated the association between metal allergy, defined by a positive

patch test reaction against common metal allergens, and revision surgery in patients who underwent knee arthroplasty.

Methods: The nationwide Danish Knee Arthroplasty Register, including all knee implanted patients and revisions in Denmark after 1997 (n=46,407), was cross-linked with a contact allergy patch test database from the capital area of Copenhagen (n=27,020).

Results: A total of 327 patients were registered in both databases. The prevalence of contact allergy to nickel, chromium and cobalt was comparable among patients with and without revision surgery. However, in patients with two or more episodes of revision surgery, the prevalence of cobalt and chromium allergy was markedly higher. Metal allergy diagnosed prior to implant surgery appeared not to increase the risk of implant-failure and revision surgery.

Interpretation: While we could not confirm that a positive patch test reaction to common metals is associated with complications and revision surgery following knee arthroplasty, metal allergy might in selected cases be a contributor to the multifactorial pathogenesis of implant-failure. In those with multiple revisions, cobalt and chromium allergy seem to be more frequent.

P05.04      Hang Nguyen      CONSEQUENCES OF MUTATION TO GLN923 FOR NA<sup>+</sup> AND K<sup>+</sup> BINDING  
Nielsen      IN NA<sup>+</sup>/K<sup>+</sup>-ATPASE

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In the recently published crystal structure of the Na<sup>+</sup>/K<sup>+</sup>-ATPase at 2.8Å resolution in a form preceding the E1P conformation with three Na<sup>+</sup> occluded (1), Gln923 of M8 together with Thr774 of M5 and other adjacent amino acid residues are involved in the formation of the third Na<sup>+</sup> binding site. The side chains of Gln923 together with Thr774 form a rigid wall comprised of a hydrogen bonding network involving, in addition, Tyr771 of M5, Gln854 of M7, and Asp926 of M8, creating a binding cavity fitting a Na<sup>+</sup> ion.

The exact functional roles of Gln923 have yet to be explored. Hence, expression of Gln923 mutants for functional analysis was previously attempted using ouabain selection methodology with mammalian cells, but the Gln923 mutants failed to confer ouabain resistance to the cells, thus precluding a detailed functional analysis. It could, nevertheless, be concluded from this work that Gln923 is essential for the overall activity of the Na<sup>+</sup>/K<sup>+</sup>ATPase (2).

In this study we have substituted Gln923 (Gln925 in the rat α1 enzyme used) with Ala, Glu, Leu, Ile, and Tyr and have been able to transiently express these mutants at a sufficiently high level for functional analysis of the partial reaction steps using siRNA to knock down the endogenous enzyme, as recently described for other inactive mutants (3), and we will report on the apparent affinities for binding of Na<sup>+</sup> and K<sup>+</sup> as derived from

the effects of these ions on the amount of phosphoenzyme formed by the mutants.

1. Kanai et al. Nature 2013, 502: 201-206

2. Imagawa et al. J. Biol. Chem., 2005, 280:18736-18744

3. Beuschlein et al., Nature Genetics, 2013, 45: 440-444

P05.05      Signe Kierkegaard      THE HAFAI-COHORT: OUTCOME AFTER ARTHROSCOPIC TREATMENT OF PATIENTS IN HORSSENS AND AARHUS WITH FEMORAL ACETABULAR IMPINGEMENT, DESIGN OF A PROSPECTIVE COHORT STUDY

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Background: Femoral acetabular impingement (FAI) is caused by an abnormality in the acetabular shape or orientation (Pincer) by a shape abnormality in the proximal femur (Cam) or by a mix of the two conditions. FAI causes repeated minor damage to the labrum and edge of the acetabulum. The damage to the joint is proposed to lead to osteoarthritis (OA) of the hip, but whether FAI is a cause or result of OA is discussed. Surgery can reduce symptoms caused by Cam or Pincer impingement and may prevent future damage to the hip joint. However, different surgical techniques are used, and only few long-term studies of the surgery exist. The latest reviews conclude that 1) we are not confident if surgery is effective for this patient group, 2) we don't know how surgery changes functional performance for the patients and 3) it is unknown how FAI affects the patients in a long-term perspective.

The aim of this prospective cohort study is to evaluate patients before and 6 and 12 months after arthroscopic surgery for FAI and compare the results to people without hip problems.

Methods: Sixty patients with FAI and 30 persons without hip problems will be included. Pre- and postoperatively, patients will be evaluated by CT-scans. All participants will have their hip flexor and extensor muscle strength assessed and have performed kinetic and kinematic analyses of daily activities with 3D motion capture. Further, self-reported questionnaires on hip-related pain, quality of life and sports activities will be collected. Finally, participants will have their daily physical activity monitored for four consecutive days.

Ethics: Approved by the Central Denmark Region Committee on Health Research Ethics (file no. 1-10-72-239-14).

P05.06      Stine Mikkelsen STABILITY CLUSTER LINKS HYDROPHOBIC GATE TO K873 IN ATP8A2

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ATP8A2 is a P4-type ATPase, a "flippase" that translocates amino-phospholipids such as phosphatidylserine (PS) and phosphatidylethanolamine (PE) from the exoplasmic to the cytoplasmic side of the plasma membrane. This flippase has similar mechanistic characteristics as the ion-translocating P2-type ATPases, though it catalyzes the transport of a much larger substrate, an enigma referred to as the "giant substrate problem". Recently, based on mutational analysis and molecular dynamics we have identified a hydrophobic gate in a groove surrounded by M1, M2, M4 and M6. A plausible water filled pocket moves in the groove when the enzyme shifts between the two states E2P and E2, and the amino-phospholipid headgroup may be located in the pocket during the transport, with the lipid tail being dragged along, jutting out into the lipid bilayer, the so-called "credit card model". Hydrophobic residues, especially I364 in M4, surrounding this pocket are involved in releasing the substrate in the transformation of E2 to E1 state. Previously, K873, located in M5, was found involved directly or indirectly in defining the substrate affinity in ATP8A2. In the present work, we identify a stability cluster harboring key residues in the center of the enzyme important for linking M5 through K873 to M4 and M6. This stability cluster supposedly allows M4 to act as a pumping rod during enzyme reaction cycle. We find that mutation of residues in this stability cluster affects the substrate affinity, as previously shown for K873. Hence, the stability cluster appears important in linking the hydrophobic gate to K873 in M5.

P05.07      Mia Børsmose      VALIDATION OF BIOMARKERS ASSOCIATED WITH METASTASIS IN  
Trip      BLADDER CANCER

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Background: Each year approximately 1700 people are diagnosed with bladder cancer (BC) in Denmark. The disease can at the time of diagnosis present itself as non-muscle invasive (NMIBC) (stages Cis, Ta and T1) or muscle invasive (MIBC) (stages T2-4). Roughly 25% of the patients have MIBC at the time of diagnosis. The treatment for non-metastasized MIBC is radical cystectomy; however if the disease has metastasized prior to surgery, patients should be treated with neoadjuvant chemotherapy. Biomarkers that may help identify metastatic disease would therefore be of great value for clinicians when selecting the patients who may benefit from e.g. neoadjuvant chemotherapy.

**Methods:** The aim is to construct a tissue microarray (TMA) with material from patients diagnosed with urothelial cancer (stage  $\geq T1$ ) who have undergone radical cystectomy at the Department of Urology at Aarhus University Hospital between 2009 and 2014. Included patients have not received chemotherapy nor radiation therapy prior to surgery. In the TMA we will also include lymph nodes from the patients with lymph node metastasis. Our plan is to use immunohistochemistry and in-situ-hybridization on TMA sections, to try and validate several biomarkers which in previous studies have been shown to be associated with aggressiveness and metastasis.

**Results:** 195 patients, 45 with concomitant lymph node metastasis, have been included and the TMA is currently under construction. We will start working with the staining of the TMA sections at the end of 2014. Hopefully our results will contribute to better diagnosis and eventually improved and more targeted treatment for patients with bladder cancer.

P05.08      Søren Skaarup    SAFETY AND QUALITY OF ULTRASOUND-GUIDED INTRALYMPHATIC ALLERGEN SPECIFIC IMMUNOTHERAPY

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**Introduction:** Allergen specific immune therapy (AIT) is the only causal treatment of allergy. The treatment is time-consuming and expensive. A new way is direct delivery of allergen into lymph nodes (ILIT). This reduces treatment from 3 years to 2 months. It is important that allergen is delivered precisely into the lymph nodes. We investigate the clinical and immunological changes in a double-blinded randomized placebo controlled trial that is still ongoing. This is a report on quality of ultrasound-guided injections and adverse effect.

**Methods:** We treated 36 grass allergic patients with ultrasound-guided intralymphatic injections with ALK phleum pratense. They were randomized to receive either 3 allergen injections or 3 placebo injections. We recorded adverse events 1 hour after each injection and at a visit one week later. We graded the quality of the injection with a 5-point scale.

**Results:** 79% of the injections had good quality. There was an increase in the quality of injection with operator experience. The success was 69% for the first injection, 75% for the second, and 94% for the third. Of the 108 injections, 12 patients had adverse event. 1 mild acute allergic reaction. 7 localized reactions with redness, edema, and itching. 4 mild late reactions with headache and muscle tenderness.

**Discussion:** Performance of ILIT improves with practice. The trial is still blinded, and we do not know if the adverse effects were result of allergen injection. There seems to be an association between allergic adverse

events and low quality injections.

Conclusion: Intralymphatic ultrasound-guided delivery of AIT is a safe treatment. Quality of injections improves with experience of the operator.

- P05.09      Lene Maria Ørts      THE VALUE AND FINDINGS OF EARLY SPIROMETRY IN TWO DIFFERENT SETTINGS
- L.M. Ørts<sup>1</sup>, A. Løkke<sup>2</sup>, A.L. Smidt Hansen<sup>1</sup>, T. Lauritzen<sup>1</sup>, A. Sandbæk<sup>1</sup>*
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- Aim: The aim of this PhD project is to investigate the value of spirometry performed as a part of preventive health checks and if impaired lung function detected by spirometry can be used as a predictor for development of Chronic Obstructive Lung Disease (COPD).
- Methods: Spirometry data from Check your Health Preventive Program (CHPP) and Ebeltoft Health Promotion Study (EH) will be included. In CHPP (2012 to 2017), citizens of Randers municipality (n= 26,216), aged 30-49 years, are invited to attend a health check and a follow-up consultation at their general practitioner. In EH, 1,507 citizens of Ebeltoft municipality, aged 30-49 years, attended a health check and a follow-up consultation at their general practitioner.
- Study I: In a cohort study based on data from CHPP in the period 2012-13 (n=10,511), the prevalence of impaired lung function is examined. Medicine usage and related government spending will be evaluated one year after examination.
- Study II: In the CHPP, 1,500 citizens are randomized in two groups: health check with or without spirometry. The primary outcome measures are participation rate and smoking status one year after spirometry. The secondary outcome measures are mental and physical health.
- Study III: In a cohort study based on data from EH (1991, 1996, and 2006), the prevalence of impaired lung function is investigated. It is also investigated if impaired lung function is a marker for development of lung disease (primarily COPD) over time.
- Perspectives: The results from the present PhD project are expected to contribute with important knowledge about the value of early spirometry in primary health care.

- P05.10      Eva Boysen      BLOOD SAMPLE MONITORING OF EGFR M+ LUNG CANCER
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**Background:** In non-small celled lung cancer 10-15% of the patients harbor a mutation in the tumor's epidermal growth factor receptor (EGFR M+). This receptor is the target for treatment with erlotinib. Identification of EGFR M+ is done on a biopsy, which can be difficult to retrieve. A new blood based test identifies EGFR M+ in plasma, which makes it possible to monitor the level of EGFR M+ in the patient's blood during treatment. This enables both a closer monitoring of the treatment with erlotinib and a closer study of the resistance mechanisms that inevitably develop during treatment. A pilot study demonstrated that the quantity of EGFR M+ in plasma correlates to the response to treatment and that resistance-causing mutations can be identified in the blood.

**Method:** A multicenter collaboration allows us to identify 200 EGFR M+ patients in a two-year period. A biopsy and blood sample will be retrieved before treatment with erlotinib is started. During treatment the patient will be monitored prospectively with blood samples every 3<sup>rd</sup>-6<sup>th</sup> week. If EGFR M+ levels rise or resistance mutations emerge clinical action will be taken.

**Aim:** We expect that our results will validate that mutations can be detected and quantified via blood samples and that this can be used in a clinical setting to monitor the effect of erlotinib treatment. This way of monitoring will make it possible to identify disease progression in an earlier stage than by CT scans alone allowing local treatment and thus - hopefully - an increase in progression free survival. Additionally, the sampling of biological material makes it possible for us to further investigate the biology of resistance.

P06.01      Thorsten  
Kamlarczyk  
Rasmussen

#### PROCEDURE-RELATED REDUCED AUTONOMIC RESPONSE DURING THE VALSALVA MANOEUVRE

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**Background:** The Valsalva manoeuvre (VM) is a central test in the diagnosis of autonomic dysfunction. The outcome is the cardiovagal changes in heart rate and the cardiovascular adrenergic changes in blood pressure. Despite the fact that many patients are unable to hold the pressure at the suggested level of 40 mmHg for 15 seconds these external factors are not routinely recorded or reported. Thus, there is a risk of a procedure-related reduced autonomic response and a risk of incorrectly diagnosing autonomic dysfunction.

**Hypothesis one:** The cardiovagal and cardiovascular adrenergic responses to VM performed within limits of normal variation in the clinical setting are reduced at lower expiratory pressure and at a shorter duration of the test.

**Hypothesis two:** Parkinson patients are not able to perform the VM at the

same pressure and duration as age-, gender- and BMI-matched controls.

Material and methods (hypothesis one): Forty healthy subjects with a normal standardized autonomic reflex testing are included. Healthy controls perform the VM randomly at 40 and 30 mmHg expiratory pressure for 15 and 10 seconds. Beat to beat heart rate, blood pressure, stroke volume, cardiac output, total peripheral resistance, and baroreceptor sensitivity are measured throughout the procedures with a Task Force Monitor. Outcome parameters: Expired pressure (AUC), Valsalva ratio, blood pressure change in late phase II and phase four. Time for blood pressure recovery.

Materials and methods (hypothesis two): Sixty patients with Parkinson disease and 60 age-, gender-, and BMI-matched controls receive identical instruction to perform the Valsalva Manoeuvre at 40 mmHg at 15 second. Outcome: Expired pressure (AUC).

P06.02      Mads Qvist  
Ebbesen

#### THE PROGNOSTIC VALUE OF QUANTITATIVE ELECTRO- ENCEPHALOGRAPHY IN COMATOSE NEUROSURGICAL PATIENTS

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Background: When assessing the prognosis for comatose neurosurgical patients the clinician relies to a large extent on the EEG-reactivity to pain, auditory and visual stimuli. This evaluation is based on a qualitative visual method for assessment of changes in the EEG upon stimulation.<sup>1</sup> This opens up for a certain degree of inter-observer variation, as two evaluators may have different opinions. The aim of this study is to investigate if a more objective quantitative assessment of EEG-reactivity is possible in these patients.

Methods: The patients are comatose patients admitted to the neurosurgical intensive care unit and have had standardized pain, sound and light stimulations done during a 24-hour EEG-monitoring. The data is analysed with NicoletOne version 5.82. Reactivity is measured as the ratio of power of the EEG-activity between a 30 second epoch of stimulation and the 30 second epoch of rest immediately before. The EEG-activity is assessed by a power spectrum analysis, which calculates the power of the  $\delta$ ,  $\theta$ ,  $\alpha$  and  $\beta$  frequency bands at each EEG electrode. After 3 months, we evaluate the patients' outcome from patient reports. We use the Glasgow Outcome Scale for outcome evaluation.

Results: We expect that patients with reactivity to stimuli will perform better at 3 months compared to patients without reactivity.

Conclusion: There is ongoing EEG-analysis in order to evaluate optimal stimulation and analysing methods. For now no data are available on 3



month outcome.

References: 1. Logi, F., Pasqualetti, P. & Tomaiuolo, F. Predict recovery of consciousness in post-acute severe brain injury: the role of EEG reactivity. *Brain Inj.* 25, 972-9 (2011).

P06.03      Ellen Lund      NO ASSOCIATION OF POLYMORPHISMS IN THE SEROTONIN  
Schaldermose      TRANSPORTER GENE WITH THERMAL PAIN SENSATION IN HEALTHY  
INDIVIDUALS

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Background: Recent studies have suggested an association between genotypes affecting the expression of the serotonin transporter and thermal pain perception. The aim of this study was to investigate differences in thermal and mechanical pain perception in two groups of healthy volunteers according to their genotype, associated with either high (n = 40) or low (n = 40) expression of the serotonin transporter. Cold and warm detection and pain thresholds, pressure pain threshold and pain responses to topical application of capsaicin and vehicle control (ethanol) and cold, warm and pain sensations to single or alternating stimuli with cold (20°C) and warm (40°C) temperatures (known as the thermal grill) were determined.

Results: No significant differences in detection and pain thresholds for cold and warm temperatures, presence of paradoxical heat sensation, pressure pain threshold and pain responses to suprathreshold thermal stimuli were observed. There was also no difference in capsaicin-evoked ongoing pain and secondary hyperalgesia between the two genotype groups (p > 0.4), also when subdivided by gender (p > 0.17). In addition, there were no significant differences in the perception of the thermal grill between the two genotypes (p > 0.5), also when subdivided by gender.

Conclusions: Genotypes associated with high or low expression of the serotonin transporter were not associated with thermal pain thresholds, pressure pain threshold, pain after capsaicin application or responses to the thermal grill.

The present results do not support that the investigated genotypes play a major role in thermal pain perception among healthy individuals.

P06.04      Trine Ellegaard      PATIENT CONTROLLED ADMISSIONS IN PSYCHIATRY - A NATIONAL  
EXPLORATIVE STUDY OF 'USER-CONTROLLED BEDS'

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Background: Improved patient involvement increase the quality of health benefits and improve the experienced efficiency of healthcare services in patients and staff. Patient-controlled admission (PCA) is a new initiative in Denmark regarding patient involvement. Psychiatric patients meeting certain conditions are offered a contract, which give them the right to initiate a short admission at a psychiatric hospital. A total of 21 user-controlled beds have been implemented at psychiatric hospitals in the five Danish regions.

Research shows that brief admissions can be effectively used in psychiatry. Patients with the possibility of PCA report improved feeling of control and safety and that they are able to get help before worsening of their symptoms. They seem to start using more active coping strategies to manage their disorder. A study showed that the total number of days admitted to hospital decreased with 33% and the number of days, patients were subjected to coercion was almost halved.

Aim: To describe patients' and healthcare professionals' experiences with PCA and develop an exploratory model regarding patient controlled admissions as a method. Furthermore to describe the patient group who uses PCA, and why they chose to submit themselves.

Method: The project obtains three sub-studies, which are complementary exploratory studies but not integrated.

Sub-studies 1 & 2: Grounded theory (GT) studies of patients' (1) and healthcare professionals' (2) experiences with PCA, which should contribute to develop an exploratory model. Data is collected from focus groups, interviews and observations.

Sub-study 3: An explorative questionnaire survey among patients and healthcare professionals.

P06.05      Anne Sofie Vinther      INSULIN-LIKE GROWTH FACTORS IN THE CEREBROSPINAL FLUID FROM PATIENTS WITH DEMENTIA

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The global prevalence of dementia is close to 36 million (2010) and the costs account for 1% of the world's GDP. Furthermore, Alzheimer's disease International predicts the number to double in the next 20 years, which will strain the current healthcare systems and national economies

The most common cause of dementia is Alzheimer's disease. The pathogenesis of Alzheimer's disease remains elusive. Thus, there is a need to increase our understanding of the mechanisms leading to Alzheimer's disease. A better understanding of the disease may enable an earlier diagnosis and more importantly, a causal treatment of Alzheimer.

In this project, we collect spinal fluid and blood samples for analyses of the IGF-system in patients with dementia. The concentrations of IGF-I and -II will be measured with validated in-house analyses. Furthermore, we will use a unique technique, whereby it is possible to measure the bioactivity of IGF-I and -II in the cerebrospinal fluid.

P06.06	Alexander Juhl Andersen	POST MASTECTOMY PAIN SYNDROME - CLASSIFICATION, PREVALENCE AND RISK FACTORS
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**Patients and methods:** All women having undergone a unilateral mastectomy at Aarhus University Hospital in the period 2009 to 2013 were screened for eligibility. Patients with active cancer and patients having received a breast reconstruction were excluded. All included patients were sent a study specific questionnaire with 36 questions pertaining to pain after breast surgery, as well as the validated painDETECT® questionnaire. Further data was obtained from the Danish Breast Cancer Group database and the electronic patient records.

Results: This is an on-going study. A total of 315 women fulfilled the inclusion criteria. At the time of submission of this abstract, the response rate was 72%.

Significance and perspectives: A large component of the PMPS may be of neuropathic origin. Neuropathic pain is characterized by damage to the peripheral nerves and the pain can remain for years after the surgical wound has healed, causing severe debilitation for the patient. Unfortunately, neuropathic pain responds poorly to standard pain treatment regimens and may even worsen over time. Therefore, it is important to characterize neuropathic pain components in order to secure the best alleviation for the individual patient.

P06.07      Kathrine Dyhr      IMPACT OF PSYCHIATRIC DISORDERS ON INTENSIVE CARE ADMISSION,  
Lycke                              QUALITY OF CARE, AND MORTALITY AFTER COLORECTAL CANCER  
SURGERY

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Background: Psychiatric patients generally have higher mortality than the general population. Although cancer incidence is lower among patients with psychiatric disorders, mortality following cancer is higher among psychiatric patients than in the general population. This could be due to lower quality of care.

Aim: To assess whether psychiatric illness among postoperative colorectal cancer (CRC) patients is associated with higher rates of ICU-admission, lower quality of surgical and intensive care, and higher 30-day mortality.

Methods: Nationwide cohort study of all postoperative CRC patients in 2005-2012 (n=22,308) using medical registries. We obtained data on previous psychiatric illness, such as psychiatric diagnoses (five years prior to the operation date) and/or redeemed prescriptions for psychoactive medication (one year prior). The quality of care is assessed using quality indicators from The Danish Colorectal Cancer Group Database and the Danish Intensive Care Database, including postoperative complications, readmission to ICU and capacity transfer. We will estimate ICU-admission rate within 30 days from operation date, the proportion of each of the quality indicators, and 30-day mortality comparing postoperative CRC patients with psychiatric illness to CRC patients without psychiatric illness. Results will be adjusted for age, gender, somatic comorbidity and other covariates including type of admission, cancer stage and length of hospital stay.

Perspectives: We expect to contribute with data on the impact of psychiatric disorders on quality and outcome of surgical and intensive care. This could guide quality improvement initiatives leading to lowering the mortality.

- P06.08      Kirstine      NON-URGENT 112-CALLERS - WHO ARE THEY, AND WHAT HAPPENS TO  
Krushave Lehm THEM?

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Prehospital Emergency Medical Services

Background: In Denmark, the emergency number is 112. Health care professionals in the emergency medical communication centres (EMCCs) handle calls on medical emergency and decide the necessary response depending on the level of emergency. There are five levels of emergency (A-E) according to the Danish Index. A is life threatening, and E is not life threatening or serious. Emergency level E-patients do not receive an ambulance but are referred to other help or given advice. This form of categorization of 112-callers was not implemented in Denmark until 2011, and the unique civil registration number on these patients was not consequently registered in the beginning. To our knowledge, no prior studies of Danish E-patients exist and therefore knowledge of their characteristics is sparse.

Aim: The aim of the study is to investigate the characteristics of E-patients in Central Denmark Region.

Methods: This study is a retrospective cohort study of E-patients calling the EMCC in the Central Denmark Region during a 12-month period (August 2013 - July 2014). It is based on linkage of electronically collected data from the EMCC dispatch software and data from three Danish national registries. A control group from the general population, who has not dialed 112, will be used for comparison of visits to general practitioners, emergency room visits, hospital admissions and mortality rate.

Perspectives: We expect the study to illuminate the not yet known characteristics of Danish E-patients. It may also provide background for future research and triage guidelines.

- P07.01      Laura Sommer      HEART FAILURE IS THE LEADING CAUSE OF DEATH THE YEAR AFTER  
Hansen      CARDIAC SURGERY REGARDLESS OF PREOPERATIVE HEART FUNCTION

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Introduction: Mortality is a frequently used outcome parameter in cardiac surgery, whereas reports describing cause of death are sparse.

Design: A multicenter registry-based descriptive cohort study including all adult patients who underwent open heart-surgery at Aarhus, Aalborg and Odense University Hospitals during the period April 1, 2006 - December 31, 2012.

Results: 11,988 patients was identified (8,654 men), age 69(62;76) years, range [15-97]. Within 1 year from surgery, 802 patients died (512 men),

age 75(68;80) years, range [24-97]. Leading cause of death was cardiac (38%). 50% of cardiac deaths was categorized as either heart failure or cardiac shock. In the preoperative assessment of heart function 37% of these patients were categorized as having normal left ventricular function (EF>50%), 27% as having mildly to moderately impaired left ventricular function (EF 30%-50%), and 36% as having severely impaired left ventricular function (EF<30%).

Discussion: Despite surgery, cardiac disease accounted for 38% of deaths the year after surgery and 50% could be attributed to heart failure. 54% of these patients were preoperatively assessed as having either normal or only mildly to moderately reduced EF. Recent studies have demonstrated a depressed systolic heart function at least 30 days after on-pump surgery. Although one of the studies found heart function to be restored after 6 months, our results imply that it may prove fatal if disregarded.

Conclusion: Regardless of preoperative heart function, heart failure is consistent leading cause of death, demonstrating the need for further studies concerning postoperative assessment of heart function.

P07.02      Jeppe  
Bakkestrøm  
Rosenbæk

THE EFFECT OF SODIUM NITRITE ON BLOOD PRESSURE, GLOMERULAR FILTRATION RATE AND FRACTIONAL SODIUM EXCRETION IN HEALTHY SUBJECTS

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Background: Recent research has shown that sodium nitrite is readily converted to nitric oxide (NO) by enzymes in vivo and exerts a vasodilating effect. Previous studies based on nitric oxide synthase inhibition indicate a natriuretic effect of nitric oxide. The purpose of the present study was to examine the effects of sodium nitrite on blood pressure, heart rate, GFR and fractional sodium excretion.

Methods: In a single blinded, crossover, placebo controlled dose-response study 12 healthy subjects were treated, in a randomized order, with placebo (isotonic NaCl) or one of three doses of sodium nitrite 40, 120 or 240 µg/kg/hour for two hours. Each examination was preceded by 4 days standardized diet. The subjects were supine and water loaded throughout the day. Before, during and after sodium nitrite administration we measured diastolic, systolic and mean arterial blood pressure (DBP, SBP and MAP), heart rate, GFR by chrome-EDTA clearance and fractional sodium excretion.

Results: The highest dose of sodium nitrite reduced fractional sodium excretion by 0.0032 95%CI (0.0006;0.0059), SBP by 4.5 mmHg (0.5;8.5), DBP by 3.8 mmHg (0.9;6.7) and MAP by 4.0 mmHg (1.2;6.8) compared to placebo. There was no effect on heart rate or GFR.

Conclusion: In supine, water loaded subjects a two hour infusion of 240 µg/kg/hour sodium nitrite exerts an antinatriuretic and hemodynamic effect on the measured parameters.

- P07.03      Astrid      ECONOMIC EVALUATION OF REMOTE ISCHAEMIC CONDITIONING AS AN  
Drivsholm Sloth      ADJUNCT TO PRIMARY PERCUTANEOUS CORONARY INTERVENTION IN  
PATIENTS WITH ST-ELEVATION MYOCARDIAL INFARCTION: A STUDY  
PROTOCOL

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Background: Ischaemic heart disease is associated with high medical care costs worldwide. Remote ischaemic conditioning (RIC) is a strategy, using brief episodes of ischaemia distant from the heart to protect against myocardial ischaemia-reperfusion injury. The stimulus can be applied in a simple, low cost manner with a dedicated device performing cycles of alternating inflation and deflation of a blood-pressure cuff. Recently, RIC has been demonstrated to improve long-term clinical outcomes in patients undergoing coronary artery bypass grafting and elective or primary percutaneous coronary intervention (pPCI). Given the large number of patients, who are potentially candidates for RIC, an economic evaluation of the cost-effectiveness of this intervention may contribute in the decision making, whether RIC should be implemented in treatment guidelines.

Aim: The aim of this study is to evaluate the cost-effectiveness of RIC as an adjunct therapy before pPCI in patients with STEMI from the perspective of a Danish healthcare system.

Design: Economic analysis of a randomised controlled study.

Participants: Between February 2007-November 2008, 333 patients with suspected STEMI were randomised during ambulance transport to the hospital for pPCI with (n=166) or without (n=167) RIC. Patients were followed until death, emigration or January 2012, whichever occurred first.

Primary outcome measure: Incremental cost-effectiveness ratio (ICER) = difference in mean medical care costs between treatment groups/difference in major adverse cardiac and cerebrovascular event (MACCE)-free survival between treatment groups.

- P07.04      Adrian Bauer      FOURTEEN YEARS OF MINIMAL INVASIVE EXTRACORPOREAL  
CIRCULATION (MIECC) AND STILL OPEN QUESTIONS?!

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Fourteen years after introduction and intense investigation of Minimal invasive Extracorporeal Circulation (MiECC) leading to a Class I, level A for

reducing haemodilution and a Class IIA, level B recommendation for an effective attenuation of the systemic inflammatory response, the application of MiECC has still a very low penetration in cardiovascular perfusion. One reason for this niche status could be the lack of understanding of the scientific community in identifying from where the potential advantages arise. This fact is due to several elements acting both interactively and independently, e.g. coated surfaces, closed systems, anticoagulation strategies, shed blood separation and reduced priming volumes. To date, no investigation has been carried out to examine these differences separately including alterations compared to conventional open perfusion circuits. This study project aims at doing the first step to a better understanding beyond investigating only limited alterations and modifications of MiECC to potentially gain a deeper understanding of MIECC. The research project, MiECC-2016, will investigate open questions regarding anticoagulation strategy, safety features, and functionality. The first study will focus on the inflammatory response and the influence of shed blood separation. The second series investigates the behaviour of microair in MiECC procedures in comparison to conventional systems while the last study aims at finding a recommendation of the best anticoagulation strategy for MiECC. Finally, MiECC-2016 could contribute to a better understanding of MiECC and potentially opens a path for this technology out of its current niche existence.

P07.05      Bodil Gade  
Hornstrup

NOCTURNAL BLOOD PRESSURE IN CHRONIC KIDNEY DISEASE, HYPERTENSION AND OBSTRUCTIVE SLEEP APNEA - CENTRAL AND PERIPHERAL 24-HOUR BLOOD PRESSURE MEASUREMENTS

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Background: In Denmark, approximately 1 million people suffer from hypertension. Untreated or insufficiently treated hypertension results in increased mortality and morbidity due to complications, such as stroke, acute myocardial infarction, congestive heart failure or chronic kidney disease. Recent studies have shown that increased nocturnal blood pressure and / or non- dipping are important prognostic factors for cardiovascular disease. Possible explanations to this are obstructive sleep apnea (OSA), impaired kidney function and the method used to measure 24 h blood pressure.

Methods: In case control studies, we will examine patients with chronic kidney disease, patients with hypertension and healthy subjects as control group. They will undergo 24 h blood pressure measurements both central and peripheral, sleep analysis to determine the frequency and severity of OSA, blood and urine samples. Results from patients and healthy subjects will be compared to determine correlations between degree of kidney disease, degree of hypertension, possible presence of OSA and difference in the central and peripheral 24 h blood pressure.



In interventional studies we will treat patients with OSA and kidney disease, OSA and hypertension with CPAP (continuous positive airway pressure) for 3 months to examine the effects of this treatment on kidney function and blood pressure.

Perspectives: The project is designed to investigate the relative importance of obstructive sleep apnea, impaired kidney function and the method used to measure 24 h blood pressure in patients with elevated nocturnal blood pressure and / or non - dipping.

P07.06      Dmitrii Kamaev CELLULAR FUNCTION OF THE  $\text{Ca}^{2+}$ -ACTIVATED  $\text{Cl}^-$  CHANNEL PROTEIN - TMEM16A - IN THE ARTERIAL WALL. THE STUDY FROM KNOCKOUT MICE

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Calcium-activated chloride channels (CaCCs) are suggested to participate in excitation-contraction coupling in the vascular wall by linking membrane depolarization and  $[\text{Ca}^{2+}]_i$  in smooth muscle cells. TMEM16A is thought to form CaCCs. SiRNA-induced knockdown of TMEM16A in rat mesenteric small arteries suppressed the agonist-induced depolarization and contraction. Since the  $\text{K}^+$ -induced depolarization was not affected but the contraction was still reduced in comparison with the controls, we suggest that TMEM16A knockdown reduces either activity or expression of L-type  $\text{Ca}^{2+}$  channels (LTCC). Accordingly, LTCC mRNA expression was reduced in TMEM16A-downregulated rat small mesenteric arteries. Moreover, co-immunoprecipitation and proximity ligation assays suggest a physical interaction between TMEM16A and LTCC.

We plan to study this putative interaction between LTCC and TMEM16A proteins at the expression and functional levels by co-expressing these proteins in HEK-293 cells and in studies in the arterial wall in situ. The systemic circulatory role (blood pressure, ECG) of TMEM16A will be studied in smooth muscle-specific knockout of TMEM16A. Agonist-induced arterial contractility,  $[\text{Ca}^{2+}]_i$  and membrane potential changes in arteries from these mice will be compared with matching wild type. Whole cell  $\text{Ca}^{2+}$ -dependent  $\text{Cl}^-$  current will be measured in voltage-clamp studies on freshly isolated smooth muscle cells. The mRNA expression of LTCC and its subcellular localization will be studied in arteries from knockout mice in comparison with the control.

P07.07      Tinne Tranberg MECHANICAL CHEST COMPRESSIONS IMPROVE QUALITY OF CPR IN OUT-OF-HOSPITAL CARDIAC ARREST

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**Aim:** To evaluate CPR quality provided by the LUCAS-2 (LUCAS-2 chest compression system) compared with manual chest compression in a cohort of out-of-hospital cardiac arrest (OHCA) cases.

**Methods:** In a prospective study conducted in the Central Denmark Region, the Emergency Medical Service attempted resuscitation of 155 non-traumatic OHCA patients occurring from April 1<sup>st</sup> 2011 to February 1<sup>st</sup> 2013. The 155 OHCA patients were all treated with LUCAS-CPR after an episode with manual-CPR. The CPR quality was evaluated using transthoracic impedance measurements collected from the LIFEPAK 12 defibrillator, and the effect was assessed in terms of no-flow fraction (the fraction of time during resuscitation in which the patient is without spontaneous or artificial circulation).

**Results:** The median total episode duration was 21 minutes (interquartile range 13 to 34 minutes). The episode with LUCAS-CPR was significantly longer compared with the manual chest compression episode (13 minutes vs. 5 minutes,  $P < 0.001$ ). The no-flow fraction was significantly lower during LUCAS-CPR (16%) compared with manual compressions (35%) showing a difference of 19% (95% CI: 16% to 21%;  $P < 0.001$ ). Compared with manual chest compressions the average compression rate during LUCAS-CPR was performed according to the current Guidelines (102/minute vs. 24/minute,  $P < 0.001$ ). The average number of chest compressions delivered per minute were significantly higher during LUCAS-CPR compared to manual compressions (94/minute vs. 74/minute,  $P = 0.012$ ).

**Conclusion:** LUCAS-CPR is associated with a significant reduction in no-flow fraction compared to manual chest compressions during OHCA resuscitation.

P07.08      Willemijn  
Comuth

ADHERENCE AND THE ROLE OF COAGULATION ASSAYS IN PATIENTS TREATED WITH DABIGATRAN ETEXILATE FOR NON-VALVULAR ATRIAL FIBRILLATION (ARCADE STUDY)

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**Purpose:** To measure the level of adherence, evaluate the usefulness of different coagulation assays to measure adherence and to determine the correlation between the plasma level and the anticoagulant effect of dabigatran in patients treated with dabigatran etexilate for non-valvular atrial fibrillation.

**Methods:** Single center prospective study including a total of ca. 550 patients treated with dabigatran etexilate for non-valvular atrial fibrillation.

We will measure the level of adherence using a questionnaire, determine dabigatran plasma levels using liquid chromatography tandem mass spectrometry (LC-MS/MS) and measure the anticoagulant effect of dabigatran using different coagulation assays at different time intervals. Most studies so far have been performed in vitro with plasma samples spiked with dabigatran. In this study the present knowledge from results of coagulation assays in dabigatran spiked plasma samples will be compared to the results of coagulation assays using blood samples from real-life patients to determine if the results of studies with spiked plasma samples are directly clinically applicable.

Results: Not yet available, ongoing study.

Conclusions: Not yet available, ongoing study.

P08.01      Jens Sundbøll      PREADMISSION USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS OR ANGIOTENSIN RECEPTOR BLOCKERS AND SHORT-TERM MORTALITY AFTER STROKE: A NATIONWIDE POPULATION-BASED COHORT STUDY

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Background and aim: The prognostic impact of ACE-inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) on stroke mortality is unclear. We aimed to examine whether prestroke use of ACE-Is or ARBs was associated with improved short-term mortality following ischaemic stroke, intra-cerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH).

Methods: We conducted a nationwide population-based cohort study using medical registries in Denmark. We identified all first-time stroke patients during 2004-2012 and their comorbidities. We defined ACE-I/ARB use as current use (last prescription redemption <90 days before admission for stroke), former use and non-use. Current use was further classified as new or long-term use. We used Cox regression modelling to compute 30-day mortality rate ratios (MRRs) with 95% CIs, controlling for potential confounders.

Results: We identified 100 043 patients with a first-time stroke. Of these, 83 736 patients had ischaemic stroke, 11 779 had ICH, and 4528 had SAH. For ischaemic stroke, the adjusted 30-day MRR was reduced in current users compared with non-users (0.85, 95% CI 0.81 to 0.89). There was no reduction in the adjusted 30-day MRR for ICH (0.95, 95% CI 0.87 to 1.03) or SAH (1.01, 95% CI 0.84 to 1.21), comparing current users with non-users. No association with mortality was found among former users compared with non-users. No notable modification of the association was observed within sex or age strata.

Conclusions: Current use of ACE-Is/ARBs was associated with reduced 30-day mortality among patients with ischaemic stroke. We found no

association among patients with ICH or SAH.

P08.02      Vibeke      LEARNING AND COPING STRATEGIES IMPROVES ADHERENCE IN CARDIAC  
                 Lynggaard      REHABILITATION

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Background: Cardiac rehabilitation (CR) has a potential to reduce mortality and morbidity. However, not all patients complete CR. Patient education programs which can enhance adherence in CR are thus needed. A new patient education; learning and coping strategies (LC), was developed.

Objective: To measure the effect of LC strategies on adherence in CR.

Methods: Designed as an open 1:1 randomised controlled trial with LC strategies applied to standard CR as the intervention arm versus standard CR as the control arm. Key points in LC strategies: situated and reflexive education, individual clarifying interviews and participation of expert patients. CR program in both arms consisted of eight weeks with 24 training, and 8 education sessions. Both arms were initiated and finished with a bicycle exercise test.

Results: In total 825 patients with ischemic heart disease and heart failure entered the analysis; 413 were randomised to LC group (mean age 63 years, 76% male) and 412 to control group (mean age 63 years, 76% male). No significant baseline differences between groups were found. In LC group 340 (83%) completed the CR program defined as attendance to second exercise test compared to 312 (76%) in control group (p=0.02). Thus adherence to CR was significantly higher (9%) in LC group. In LC group 80% attended at least 18 training sessions which was significantly higher than the patients in control group where 73% attended 18 training sessions or more (p=0.023). Patients in LC group attended on average in 6.6 education sessions which was significantly more than 6.0 in control group (p=0.04).

Conclusion: Study indicates that LC strategies applied in CR improves adherence.

P08.03      Christina      OXYGEN SATURATION IN CENTRAL AND PERIPHERAL RETINAL VESSELS IN  
                 Mørup      PATIENTS WITH TREATMENT REQUIRING DIABETIC RETINOPATHY  
                 Jørgensen

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**Purpose:** Diabetic retinopathy is characterized by hyperperfusion in the macular area resulting in diabetic maculopathy, and hypoperfusion in the retinal periphery resulting in retinal ischemia that stimulates neovascularization. The purpose of the study is to investigate the difference in these perfusion changes between vessels extending into the macular area and vessels extending into the peripheral area by assessing retinal oxygenation in patients with these treatment requiring complication types.

**Methods:** Retinal oximetry (Oxymap T1, vs. 2.4.2) and diameter measurements were performed on a temporal retinal arteriole and venule extending into the macular and peripheral area as well as on the main arcade vessel in the temporal region. Images were taken in one eye from 77 patients with diabetic maculopathy (DM) and 41 patients with proliferative diabetic retinopathy (PDR) as well as in one eye from 44 healthy persons.

**Results:** Preliminary data shows no significant differences between the vessels extending into the macular area and vessels extending into the peripheral area ( $p > 0.12$  for all comparisons).

**Conclusion:** The regional differences in perfusion changes are not correlated with differences in oxygen saturation in vessels supplying macular and peripheral retinal areas. However, further analyses are required to substantiate this conclusion.

P08.04      Johan Frederik      ELEVATED PLASMA VITAMIN B12 AND RISK OF VENOUS  
Berg Arendt      THROMBOEMBOLISM IN PATIENTS WITH CANCER

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**Background:** Venous thromboembolism (VTE) is a serious complication to advanced cancer. High vitamin B12 levels may be a marker of aggressive cancer, but the association between high vitamin B12 levels and VTE risk in cancer patients has not been studied. We examined the risk of VTE among cancer patients according to plasma vitamin B12 level.

**Methods:** We will include all patients with a cancer diagnosis and vitamin B12 levels of 200-600 (reference range), 601-800 and >800 pmol/L measured up to one year prior to diagnosis during 1998-2010 from the Danish Cancer Registry and the Laboratory Information Systems Database in Northern Denmark. Data on the use of B12 supplements and co-morbidity will be obtained through the Aarhus University Prescription Database and the Danish National Registry of Patients. B12 supplemented patients will be excluded and co-morbidity will be scored according to the Charlson Co-morbidity Index. Cox proportional hazard regression model will be used to assess the risk of a VTE event. We will adjust for age, sex and comorbidity, treating death as a competing risk. Kaplan-Meier curves will be computed to assess incidence of VTE events.

**Conclusion:** High vitamin B12 levels have also been associated to VTE events in orthopaedic surgery patients. We hypothesize that elevated vitamin B12 levels are associated to an increased risk of VTE among cancer patients.

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**Background:** Cardiac resynchronization therapy (CRT) improves hemodynamics and may allow further optimization of evidence-based heart failure (HF) medication. However, undertreatment and non-adherence to medical therapy are important problems. The objective of this study was to examine adherence to HF medication after CRT implantation.

Results: Mean age was  $66 \pm 11$  years, ejection fraction  $24 \pm 6\%$ , and 79% were males. Median follow-up was 4.5 (3.1-6.8) years. Within the first year after CRT implantation; numbers of patients treated with beta-blockers (BB) (89% vs. 75%;  $P < 0.001$ ) and daily doses had increased ( $63\% \pm 37$  vs.  $51\% \pm 37$ ;  $P < 0.001$ ); also the daily doses of renin-angiotensin system (RAS) inhibitors had increased ( $78\% \pm 42$  vs.  $74\% \pm 38$ ;  $P = 0.02$ ) but the proportion of patients treated was unchanged (92% vs. 90%;  $P = 0.55$ ). During the study period, the proportion of patients who received BB and RAS inhibitors was high, 89% and 90% at 4 years respectively. Adherence to treatment with BB and RAS inhibitors remained high; 94% and 92% at 4 years respectively.

Conclusion: The proportion of patients treated with evidence-based HF medication after CRT implant is high, and adherence is maintained during long-term follow-up.

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**Purpose:** Remote ischemic conditioning (RIC) increases myocardial salvage index (MSI), whereas extended system delay reduces MSI and increases final infarct size (FIS) in patients with ST-elevation myocardial infarction (STEMI). We investigated the influence of RIC on the effects of system delay in STEMI patients undergoing primary percutaneous coronary intervention (pPCI).

**Methods:** In a prospective, single-blinded randomized controlled trial (n=251), we studied STEMI patients randomized to treatment with either pPCI alone or pPCI+RIC. RIC was performed during transport to hospital as 4 cycles of 5 min upper arm ischemia followed by 5 min reperfusion. Area-at-risk, MSI and FIS were assessed by single photon emission computerized tomography (SPECT). System delay was defined as time from emergency medical service (EMS) call to pPCI-wire. Data were obtained from EMS registries and files.

**Results:** Data for FIS and system delay and for MSI and system delay were available for 202 and 129 patients, respectively. Patients were equally distributed among treatment with pPCI alone or pPCI+RIC. Area-at-risk and system delay did not differ between patients treated with pPCI alone or pPCI+RIC (p=0.97 and p=0.91, respectively). While system delay in patients treated with pPCI alone was associated with significantly reduced MSI (p<0.01) and increased FIS (p=0.04), these associations were attenuated in patients treated with pPCI+RIC (p=0.74 and p=0.63, respectively).

**Conclusion:** RIC treatment attenuates the effect of extended system delay on MSI and FIS in STEMI patients treated with pPCI, and may prolong the window for pPCI as eligible strategy for reperfusion therapy in STEMI patients.

P08.07      Line Pedersen      THE REGULATION OF RETINAL ARTERIOLES DURING HYPOXIA ARE MODIFIED BY NO AND COX PRODUCTS.

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**Background:** Diabetic retinopathy is characterized by retinal hypoxia and consequent dilatation of the larger retinal vessels. In vitro studies of porcine retinal tissue have shown that hypoxia-induced vasodilatation is mediated by cyclo-oxygenase (COX) and nitric oxide (NO). The aim of the present study was to examine if these results could be reproduced in vivo.

**Methods:** Twenty healthy persons and twenty diabetic patients without diabetic retinopathy aged 20-55 years were examined using the Dynamic Vessel Analyzer (DVA). The resting diameter and the diameter response secondary to isometric exercise and flicker stimulation of retinal arterioles were measured before and during breathing a hypoxic gas mixture. The

examinations were performed before and during intravenous infusion with the NOS inhibitor L-NMMA and were repeated on a second study day after administration of the COX-inhibitor diclofenac as eye drops.

Results: The resting diameter of both groups was significantly increased by hypoxia ( $p < 0.0001$ ), and this was reversed by the infusion of L-NMMA. Diclofenac significantly reduced arteriolar contraction induced by isometric exercise in healthy persons ( $p = 0.04$ ) whereas preliminary data of diabetic patients point to an increased contraction in this group. In healthy persons the flicker-induced dilatation was increased by L-NMMA ( $p < 0.0001$ ) whereas hypoxia reduced the dilatation observed in diabetic patients.

Conclusion: NO and COX products are involved in the hypoxia-induced dilatation of retinal vessels. This evidence might potentially be used as a tool for intervention on diameter changes of retinal vessels in diabetic retinopathy.

P08.08      Peter Rubak      CYCLOOXYGENASE-1 AND 2 IN PLATELETS: IS THERE AN ASSOCIATION WITH IMMATURE PLATELET FRACTION AND PLATELET FUNCTION

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Background: Aspirin is used for managing cardiovascular disease, but 15% of patients develop a new cardiovascular event despite treatment. A reduced effect of aspirin is seen in patients with a high immature platelet fraction (IPF). Cyclooxygenase (COX)-1 functions as a platelet activator in all platelets and is inhibited by aspirin, but immature platelets also contain COX-2, which is not affected by aspirin.

Aim: To develop and validate an assay to assess COX-1 and 2 in platelets and to investigate associations with platelet function and IPF.

Methods: Platelet rich plasma was fixed and permeabilised with PerFix-nc. Antibodies for CD41, CD45, COX-1 and 2 were added and incubated, after which platelets were washed and diluted prior to flow cytometric analysis. Isotype controls were used as negative control. IPF and platelet function were measured with flow cytometry (Sysmex XE-5000 and NAVIOS). 30 healthy volunteers and 15 patients with primary immune thrombocytopenia (ITP) will be included in the study.

Results: Preliminary results of 2 healthy volunteers showed detectable levels of COX-1 (6-9 MFI) in all platelets, but only 3-10% platelets contained COX-2. Preliminary results of 3 ITP patients showed increased levels of COX-1 in all platelets (9-26 MFI) and fraction of platelets containing COX-2 (9-28%). Reference intervals for COX-1 and 2 will be established on healthy volunteers and presented along with investigations of associations between: Platelet function, IPF COX-1 and 2.

Conclusion: We are developing and validating an assay for assessing



COX-1 and 2 in platelets and will conclude on their association with platelet function and IPF.

P08.09 Morten Krogh Christiansen PREMATURE CORONARY ARTERY DISEASE - CLINICAL AND MOLECULAR GENETIC ASPECTS

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Upon the finishing of the human genome sequencing project in 2003, genetic research in coronary artery disease (CAD) has developed dramatically. Genome-wide association studies have identified a number of common genetic variants associated with CAD. However, each of the identified genetic variants only have minor effects on disease development per se and pooling of the known genetic variants only explain a minor percentage of the total heritability. De-novo mutations probably play a role for the development of CAD, especially among young patients. Thus, we hypothesize that exome sequencing and linkage analysis in families comprising extreme phenotype cases, can identify disease-causing genetic variants.

Based upon information from the West Danish Heart Registry, we will enroll a minimum of 120 patients who have undergone a coronary revascularization procedure before the age of 40, to participate in study 1: For all participants a pedigree analysis will be done and CAD risk factors and current preventive treatment will be entered into a registry. Healthy first degree relatives aged 30-65 years will be invited to participate in study 2: A coronary CT angiogram will be performed to quantify the degree of coronary atherosclerosis. From study 1 and 2 families demonstrating severe premature coronary atherosclerosis will be selected for exome sequencing. Subsequent genetic variants identified will be filtered on a basis of linkage analysis, gene frequency analysis, gene positioning, existing knowledge on genetic variation, and in-silico prediction tools. Causality of potential new genetic variants thus identified will be investigated in experimental studies.

P08.10 Junjing Su WAVE INTENSITY ANALYSIS IN THE PULMONARY ARTERY

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Background: Wave intensity analysis (WIA) is a time-domain technique that uses simultaneous changes in the arterial pressure and flow velocity to determine the magnitude, origin, type and timing of travelling waves in a circulation. The objective of this study was to apply WIA in the pulmonary artery (PA) to assess right ventriculo-arterial coupling in man.

Method: Right heart catheterisation was performed using a pressure and

Doppler flow sensor tipped catheter to obtain simultaneous pressure and flow velocity measurements in the PA. Recordings were made at rest as well as during Valsalva manoeuvre and handgrip exercise. WIA was subsequently applied to the acquired data.

Results: 10 patients ( $59 \pm 14$  years, 8 male) undergoing cardiac catheterisation and with normal mean pulmonary arterial pressure ( $17 \pm 3$  mmHg) and without significant cardiovascular disease or lung disease were studied. In the PA, WIA showed a forward (proximally originating) compression wave in early systole caused by right ventricular ejection and a forward decompression wave prior to closure of the pulmonary valve that decreased the arterial pressure and flow in late systole. Backward (reflecting) waves were minimal. Wave speed was  $3.0 \pm 0.9$  m/s. The wave pattern was unchanged during handgrip exercise. However, during expiration and Valsalva manoeuvre, the magnitude of the waves reduced.

Conclusion: There is minimal wave reflection in the PA in individuals without PA disease indicating well matched ventriculo-arterial coupling. We have established that WIA in the PA is feasible. WIA may contribute to a greater understanding of the pulmonary hemodynamics in patients with pulmonary hypertension.

P09.01      Rikke Elmose      VISUALIZATION OF CORONARY ARTERY CALCIFICATION AND THE  
Mols                              INFLUENCE ON PREVENTIVE THERAPY AND LIFESTYLE MODIFICATION

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Background: The relation of coronary computed tomography (CCTA) findings in symptomatic patients regarding adherence to preventive medical therapies and risk modification is unknown. The purpose of this study was to test the effect of "visualization" of coronary artery calcification and brief recommendations on cholesterol levels and other risk variables in patients with a new diagnosis of coronary artery disease (CAD).

Methods: A prospective two-center randomized controlled trial. Patients were randomized 1:1 to standard follow-up in general practice or intervention. Patients were followed for six months. The primary end-point was change in serum total-cholesterol.

Results: The study included 189 patients, aged  $61 \pm 12$  years (males 57%), and median (IQR, range) Agatston score was 166 (101-334, 70-2054). Intention-to-treat analysis showed a tendency towards a more effective absolute reduction in total-cholesterol levels in the intervention group ( $P = 0.181$ ). In a subgroup analysis excluding patients discontinuing statin therapy due to side effects ( $N = 147$ ), the 6-month reduction in total-cholesterol was more efficient in the intervention than in the control group ( $P = 0.027$ ). More patients in the control group continued smoking and unhealthy dietary behaviour. Weight loss was more pronounced in the intervention group and furthermore there was a tendency towards a higher

degree of statin adherence in the intervention group

Conclusion: Visualization of coronary artery calcification and brief recommendations regarding risk modification after CCTA in symptomatic patients with a new diagnosis of CAD has a positive effect on risk modification.

P09.02 Anni Jeppesen DOES HYPOTHERMIA AFTER CARDIAC ARREST INFLUENCE HEMOSTASIS?

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Introduction: Treatment with hypothermia in comatose survivors after out of hospital cardiac arrest improved cerebral outcome. Despite no significantly increased bleeding tendency when treated with hypothermia after cardio-pulmonary resuscitation, patients with a risk of bleeding are considered as having a contraindication to this treatment.

Objectives: To clarify whether treatment with hypothermia after cardiac arrest induced significant changes in coagulation. The specific aims were: Study 1) To investigate changes in whole blood coagulation and platelet function in comatose survivors after cardiac arrest treated with hypothermia. Study 2) To examine differences in whole blood coagulation analyses analyzed simultaneously at 33°C and 37°C.

Methods: This project included comatose patients resuscitated after cardiac arrest and randomized to either 24 or 48 hours of hypothermia (33±1°C) at the Intensive Care Unit, Aarhus University Hospital, Skejby. The patients will be included over a two-year period beginning in Marts 2013. Blood were analyzed three times with intervals of 24 hours using whole blood coagulation analyses (ROTEM®), platelet function analyses (Multiplate® Analyzer), thrombin generation, clot stability analyses, and standard coagulation and haematological analyses; INR, APTT, thrombin time, fibrinogen, antithrombin, fibrin d-dimer, hematocrit, leukocytes, and platelet count. Our power calculation estimated that study 1 and 2 should include 98 and 40 patients, respectively.

Results: Currently recruiting participants.

Conclusion: We hoped to determine how the coagulation was affected by hypothermia after cardiac arrest.

P09.03 Mia Benedicte Lykke Roest Laursen CELL MODEL FOR METABOLOMICS STUDIES OF REMOTE ISCHEMIC CONDITIONING

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Remote ischemic conditioning is a cheap, effective, and non-invasive method to protect organs against injuries caused by strokes and heart attacks. Although intensely investigated, the mechanisms of this protective phenomenon remain poorly understood and the role played by metabolites has been neglected. The present study is expected to map the changes in the metabolome of cells triggered by remote ischemic conditioning, thus, setting up the need for a reliable and reproducible cell assay. Derived from murine cardiomyocytes, the immortal HL-1 cell line has previously been used as a strong model for cardiomyocytes to enlighten a wide range of different conditions. Mimicking ischemia, HL-1 cells were, thus, placed in an oxygen free atmosphere with the growth medium replaced by an ischemic buffer depleted of glucose and with low pH. Control cells were kept at normal conditions and in the presence of a buffer containing physiological glucose and pH levels. Local ischemic conditioning was applied by short ischemia prior to long and lethal ischemia and was found to significantly reduce the amount of cell death. Following these findings, the transfer of buffer solution from conditioned to non-conditioned cells is expected to confer protection in these as well, visualizing the ability of the cells not only to be protected by local ischemic conditioning but also by remote ischemic conditioning. Subsequent analysis of the metabolome using untargeted metabolomics (LC-qTOF-MS) will provide valuable insight into the changes in the metabolome and is, thus, expected to further widen the understanding of remote ischemic conditioning.

P09.04 Jeong Shim APOE-KNOCKOUT AND ATHEROSCLEROSIS IN MINIPIGS

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Background: Atherosclerosis is by far the most common cause of ischemic heart disease and a common cause of stroke. The underlying cause of atherosclerosis is hypercholesterolemia. Mice with targeted disruption of genes involved in cholesterol metabolism, such as apolipoprotein E (APOE), develop rapid atherosclerosis and have enabled many discoveries in molecular mechanisms of atherosclerosis. However, the small size of the animals is a challenge to noninvasive imaging and it precludes research in intravascular devices, such as stents, and many histological features of human atherosclerosis are rare or absent in mouse models. The aim of this study was to create a human-sized porcine model with hypercholesterolemia and atherosclerosis by targeted disruption of APOE in Yucatan minipigs by rAAV-mediated gene targeting and somatic cell nuclear transfer. We aim to evaluate cholesterol levels (when fed high-fat high-cholesterol diet) and atherosclerosis in N=12 APOE-knockout (KO) and N=12 wild-type (WT) pigs.

Preliminary results: We found mean total cholesterol to be 9.6 mM in WT (N=4) and 15.4 mM in KO (N=7) by the age of 12 months. APOE-KO pigs were found to accumulate more ApoB-48 containing remnant particles than WT. In the thoracic aorta we found median intimal area covered with

atherosclerosis to be 12.1% (N=8) in WT and 13.5% in KO (N=8) and in abdominal aorta 7.4% in WT (N=8) and 23.9% in KO (N=8)

Conclusion: We created the first porcine model of APOE-KO. Preliminary results indicate higher total cholesterol levels and more atherosclerosis in the abdominal aorta in APOE-KO compared with WT.

P09.05 Kristian Løkke Funck ARTERIAL STIFFNESS AND COMPLICATION RISK IN TYPE 2 DIABETES

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Background: A common complication of diabetes is the disease of the blood vessels, vascular diseases, which can cause disorders like myocardial infarction, stroke and kidney failure. Arterial stiffness, a novel risk marker, may provide additional prognostic information when evaluating the risk of vascular complications in patients with type 2 diabetes.

Aim: We want to investigate 1) the association between arterial stiffness and subclinical atherosclerotic changes in the coronary arteries assessed by computed tomography (CT) and 2) the predictive value of arterial stiffness on the development of subclinical cerebrovascular changes assessed by magnetic resonance imaging (MRI) and nephropathy assessed by urine analysis.

Methods: The study population consists of 100 patients with newly diagnosed type 2 diabetes and 100 age- and sex-matched controls. The study participants were enrolled between 2008-2011 and extensively characterized i.a. with arterial stiffness (pulse wave velocity), MRI (white matter lesions and cerebral infarctions) and urine analysis (albuminuria). In this study, we will enrol the same patients in a 5-year follow-up study in order to repeat above-mentioned measurements. Furthermore, CT is used to investigate the coronary plaqueburden of the participants (Segment Involvement Score and volumina of calcified and non-calcified plaques).

Results and perspectives: This project adds new insight into arterial stiffness as a predictor of the progression of micro- and macro-vascular complications in patients with type 2 diabetes and can potentially improve risk stratification and early strategies of intervention in this patient group.

P09.06 Nils Henrik Hansson AORTIC VALVE STENOSIS AND LEFT VENTRICULAR EFFICIENCY

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Background: Aortic valve stenosis (AS) is the most common heart valve disease in the Western world characterized by gradually deterioration of the valve, heart failure and high mortality. Despite frequent assessment by echocardiography, the onset of heart failure is hard to predict.

Consequently, timing of aortic valve replacement is a challenging issue and new monitoring techniques are needed.

Aim: To determine left ventricular efficiency (LVE) in patients with different degrees of AS. LVE defined as stroke work/oxygen consumption is a potential new and more sensitive marker for the progression towards heart failure.

Methods: In a cross-sectional study design, 60 AS patients and 10 healthy volunteers will be studied to assess LVE non-invasively by cardiac magnetic resonance imaging, echocardiography and [ $^{11}\text{C}$ ]acetate positron emission tomography. Participants will be clustered into 4 study groups:

1. Asymptomatic AS (n=40), 2. Symptomatic AS and ejection fraction  $\geq 50\%$  (n=15), 3. Symptomatic AS and ejection fraction  $< 50\%$  (n=15) and 4. Health volunteers (n=10).

Results: Preliminary results from approximately 1/3 of all data suggest a gradually impaired LVE for study group 1-3 ( $p=0.031$ ) with LVE for group 1:  $28.3 \pm 5.1$ , group 2:  $27.0 \pm 5.6$ , group 3:  $21.8 \pm 2.1$  and group 4: not analysed.

Conclusion: These preliminary results suggest that LVE is a new potential marker for the heart failure process in patients with AS. Therefore, monitoring LVE could result in more accurate timing of aortic valve replacement.

P09.07      Tor Skibsted      ASSESSMENT OF VASCULOPATHY USING CORONARY FLOW VELOCITY  
Clemmensen      RESERVE AND 2D-SPECKLE TRACKING ECHOCARDIOGRAPHY DURING  
SEMI SUPINE EXERCISE TEST

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Aim: To evaluate the utility of non-invasive assessed cardiac allograft vasculopathy (CAV) in heart transplanted (HTx) patients by coronary flow velocity reserve (CFVR) and deformation capacity by 2D-speckle tracking echocardiography.

Methods: Fifty HTx-patients underwent comprehensive echocardiographic assessment of graft function during semi-supine exercise test. CAV was assessed by coronary angiograms and non-invasive Doppler coronary flow velocity reserve (CFVR). We divided patients into two CAV-groups: A: Non/mild CAV (n=33), B: Moderate/severe CAV (n=17).

Results: Patients with significant CAV had higher NYHA class ( $p<0.0001$ ) and troponin T ( $p=0.01$ ). Systolic function was impaired in the patients with

significant CAV, with reduced ejection fraction ( $p=0.03$ ) and impaired magnitude of global longitudinal strain (LV-GLS  $-12.5\pm3.5\%$  vs  $-15.5\pm2.1\%$ ,  $p=0.0005$ ). Patients with significant CAV failed to improve longitudinal deformation during exercise in contrast to patients without significant CAV (Peak LV-GLS  $-12.8\pm5.3\%$  vs  $-19.7\pm3.5\%$ ,  $p<0.0001$ ). Resting coronary flow velocity was higher in patients with moderate/severe CAV ( $p=0.004$ ), whereas peak coronary flow velocity was lower leading to reduced CFVR in patients with moderate/severe CAV ( $1.8\pm0.5$  vs  $2.8\pm0.6$ ,  $p<0.0001$ ). In order to distinguish patients with any degree of CAV ( $n=27$ ) from patients without CAV ( $n=23$ ) both CFVR, peak LV-GLS, and  $\Delta$ GLS showed good correlation with area under ROC-curve of 0.89, 0.85, and 0.90.

Conclusion: Deformation capacity in HTx patients is highly dependent on CFVR. Echocardiography during exercise and non-invasive CFVR might be helpful in the diagnosis of CAV and planning of routine angiograms.

P09.08 Sarah Holmboe

#### DIFFERENTIAL EFFECTS OF PROSTACYCLIN ANALOGUES ON RIGHT VENTRICULAR FUNCTION IN THE ISOLATED RAT HEART

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Purpose: Prostacyclin analogues are widely used in the treatment of pulmonary hypertension, but their direct effects on right ventricular (RV) function have only been sparsely investigated. The aim of this study was to compare the direct effects of different prostacyclin analogues on RV function.

Methods: Rat hearts ( $n=30$ ) were isolated and perfused with Krebs Henseleit buffer in a pressure controlled Langendorff setup. The hearts were perfused with increasing concentrations of the prostacyclin analogues epoprostenol, iloprost, treprostinil or the IP-receptor agonist, MRE-269. The dose dependent effects on RV hemodynamics were monitored using a fluid filled balloon in the RV connected to a pressure transducer. Coronary flow was monitored using an inline flow probe to confirm a vasodilatory effect of the drugs.

Results: All four drugs increased coronary flow rate in a dose-dependent manner. Treprostinil perfusion caused an increase in RV rate pressure product (RPP) when administered in clinically relevant concentrations. Supra-clinical concentrations blunted this response. Iloprost and MRE-269 did not improve RPP in clinically relevant concentrations. However, when administered in supra-clinical concentrations, iloprost and MRE-269 improved RPP. Epoprostenol showed a trend towards increasing RPP when administered in supra-clinical concentrations.

Conclusion: The prostacyclin analogues treprostinil, iloprost and epoprostenol and MRE-269 all increased coronary flow rate in the isolated perfused rat heart. Only treprostinil, iloprost and MRE-269 significantly improved RV function and solely treprostinil was effective when

administered in clinically relevant doses.

- P10.01      Wieke Haakma      VISUALIZING THE VESSELS IN POST MORTEM BODIES USING COMPUTED TOMOGRAPHY ANGIOGRAPHY
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- Aims: For centuries, the main documentation of postmortem findings has been based on the written records after an autopsy. Disadvantages of this approach are the observer-dependent manner and in some (vascular related) cases it is quite troublesome to find the exact cause of death. We hypothesize that computer tomography angiography (CTA) may overcome these problems as this method provides a storable 3D visualization of the entire vascular system.
- Methods: The study included four males and one female, aged 35-48 (mean 40 years). CTA was performed 48-168 hours after estimated time of death. The angiographic procedure was done after autopsy, where vessels in the groin and right arm were filled up with CT contrast agent using a pressure-regulated heart-lung-machine. The CT scans were performed with a Siemens Somatom Definition 64 slices CT scanner (Siemens Medical Solutions).
- Results: This CTA method provides a feasible way to visualize the vascular system. Especially in the thoracic region the smaller vessels can be clearly identified. One partial CTA in a dialysis patient, who apparently bled to death in his home shortly after dialysis, showed a leakage at the level of an arteriovenous shunt in the right upper arm under a small skin lesion.
- Conclusion: Post mortem CTA is a novel noninvasive approach to visualize the vascular system. It gives insight into vascular lesions which can be missed or difficult to obtain during autopsy procedures. We recommend performing a separate partial CTA when the subject is suspected to have vascular lesions in the extremities. We believe that CTA can provide a valuable contribution to the identification of cause of death in forensic sciences.
- P10.02      Michala Herskind Sejrs      DETECTION OF ATRIAL FIBRILLATION IN STROKE AND TCI PATIENTS
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- Purpose: In a consecutive population of patients with stroke or transient ischemic attack (TIA), we aimed 1. To validate 2-day loop recording (R.Test Evolution 4) to 2-day Holter (HR) recording (gold standard) for the



detection of atrial fibrillation (AF) of  $\geq 30$  seconds duration, 2. To determine whether short runs of AF ( $< 30$ s) or the presence of many supraventricular extrasystoles detected on HR, is associated with risk of restroke and 3. To test whether a 7-day loop recording (R .Test) detects more patients with AF than 2 days of HR recording.

Background: 15 million people worldwide and in Denmark 14.000 are each year attacked by stroke, leaving stroke as the third leading cause of death. AF is the most important cardiac cause of ischemic stroke and occurs in 2% of the Danish population. Anticoagulation will annually reduce absolute risk of 6-8 % for recurrent stroke in patients with prior stroke / TIA and AF, corresponding to 2/3 risk reduction. AK in patients with previous stroke or TIA is associated with increased risk of intracranial bleeding compared to patients without previous stroke or TIA. Anticoagulant therapy should therefore only be instituted on a truly increased risk of restroke. The R.Test is a new device, that continuously monitor and automatically analyses heart rhythm. It is much less resource demanding compared to traditional HR analysis, but the validity of the R.Test with regard to detect AF compared to HR is not known.

Methods: Prospective follow up study of 1500 patients whom within 1 week has had an ischemic stroke or TCI. Patients are followed in the Danish Stroke Registry regarding restroke. All patients will simultaneously have mounted a Holter and R.Test.

P10.03      Morten  
Thingemann  
Bøtke

#### DYSPNEA - A LETHAL SYMPTOM IN PATIENTS PRESENTING TO THE PREHOSPITAL EMERGENCY MEDICAL SERVICE

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Introduction: Electrocardiogram (ECG) based telemedicine is a cornerstone in prehospital triage of patients with suspected ST-elevation myocardial infarction (STEMI). An ECG transmitted from the ambulance is reviewed by a cardiologist on-call in case of chest pain, resuscitation from cardiac arrest, acute dyspnea of unknown origin and other suspicion of STEMI. We hypothesize that unresolved dyspnea is an independent predictor of mortality in this prehospital setting and that the mortality is higher in patients with acute dyspnea of unknown origin than in patients with chest pain.

Methods: Population based follow-up study from June 1, 2008 to January 1, 2013. Participants were 17.361 patients triaged using ECG based telemedicine in the Central Denmark Region. Mortality-data was obtained from the Danish Civil Registration System. To determine relative risks, we used a generalized linear regression model based on pseudo-observations.

Results: Of the 17.361 patients, 1.461 was triaged because of unresolved dyspnea. Adjusted for age, sex, systolic blood pressure and Charlson Comorbidity Index, 30-day mortality was higher in patients with unresolved

dyspnea than in patients with chest pain with a RR 2.55 (CI 2.09-3.10). This difference remained significant at 4 years with a RR of 1.34 (CI 1.24-1.45).

Conclusion: Unresolved dyspnea in the prehospital setting is an independent predictor of mortality and the mortality is higher than in patients with chest pain. Future research should focus on possibilities for improving early diagnosis and treatment of these patients.

P10.04      Anders Krogh      ABORTED SCD IN THE YOUNG CAUSED BY NON-ISCHEMIC INHERITED  
Brøndberg      HEART DISEASE - CLINICAL AND NEW MOLECULAR-GENETIC ASPECTS

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Background: Sudden cardiac death (SCD) by young adults and presumably healthy persons is often caused by inherited heart disease. There are two main groups of non-ischemia hereditary heart disease; cardiomyopathies and channelopathies. These conditions give a significantly increased risk of acquiring heart arrhythmias such as ventricular tachycardia (VT) or ventricular fibrillation (VF), syncope, cardiac arrest and thereby sudden cardiac death. Until now the genetic diagnostic tools, in patients with SCD or survivors after cardiac arrest, have targeted the presumed phenotype, which can be very difficult to define. This means that important genetic information is uncovered inadequately, thus preventing proper counseling and tracing of family members with the same high risk. With the introduction of Next Generation Sequencing (NGS) it is possible to sequence large quantities of genetic material compared to Sanger sequencing.

Objective: The share of patients with hereditary heart disease without ischaemic heart symptoms is underestimated. We will offer targeted NGS with a panel of 117 heart genes.

Methods:

Study 1: 15-year retrospective study. All patients less than 50 years of age admitted to the Department of Cardiology B, Aarhus University Hospital with VF/VT where ischaemia has been ruled out, are offered genetic testing with NGS. If hereditary heart disease is found relatives are offered genetic counseling.

Study 2: 1-year prospective study. Same criteria as above.

Study 3: Registry based study on catecholaminergic polymorphic ventricular tachycardia (CPVT).

Current status: including in progress.

P10.05      Christian Reuss      DO DRUGS CAUSE SUDDEN DEATH AMONG PSYCHIATRIC PATIENTS? - A

Mikkelsen      STUDY ON POLYPHARMACY AND ARRHYTHMIA

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This PhD project is part of a national forensic autopsy-based research project called SURVIVE, which aims at investigating the mortality and morbidity of psychiatric patients with a special focus on schizophrenia.

From forensic estimates, a cause of death is not found in about 15 % of the autopsies of psychiatric patients. This frequency is higher than for the general forensic population. Polypharmacy of antipsychotics, antidepressants and drugs of abuse is a very frequently phenomenon among psychiatric patients. Many of these drugs have been shown to be QT-prolonging and block the delayed repolarization potassium ion channel hERG.

One hypothesis of this project is that it is possible to prove a difference in the heart/blood ratio in different causes of death. Heart and blood samples are obtained from autopsies, and selected drugs are quantified to establish a heart-blood concentration ratio. These ratios will then be examined in relation to different causes of death. The Department of Forensic Medicine uses state-of-the-art LC-MS/MS equipment for the quantitative determination of drugs.

A second hypothesis of the project is to prove an additive or synergic effect of a combination of two QT-prolonging drugs on hERG. These investigations will be performed using a whole cell patch clamp experiment on cells overexpressing hERG. The project will be performed in cooperation with the Danish Arrhythmia Research Center at Copenhagen University.

The perspective of the project is to further clarify the cause of death among psychiatric patients, and furthermore investigate the cardiac toxicity of QT-prolonging drugs in combination.

P10.06      Sara Gaur      FRACTIONAL FLOW RESERVE DERIVED FROM CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY: VARIATION OF REPEATED ANALYSES

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Background: Fractional flow reserve (FFR) is the standard of reference for assessing the hemodynamic significance of coronary stenoses in patients with stable coronary artery disease (CAD). Non-invasive FFR derived from coronary computed tomography angiography (FFR<sub>CT</sub>) is a promising new

non-invasive method for assessing the physiologic significance of epicardial stenoses. The reproducibility of FFR<sub>CT</sub> has not yet been established.

Objective: The aim of this study was to evaluate the variation of repeated analyses of FFR<sub>CT</sub> per se and in the context of the reproducibility of repeated FFR measurements.

Methods: Coronary CT angiography (CTA) and invasive coronary angiography with repeated FFR measurements were performed in 28 patients (58 vessels) with suspected stable CAD. Based on the coronary CTA dataset, FFR<sub>CT</sub> analyses were performed twice by two independent, blinded analysts.

Results: In 21% (12/58) of the vessels FFR was  $\leq 0.80$ . The standard deviation for the difference between first and second FFR<sub>CT</sub> analyses (SD<sub>FFR<sub>CT</sub></sub>) was 0.034 versus 0.033 for FFR repeated measurements (SD<sub>FFR</sub>) (p=0.722). Limits of agreement were -0.06 to 0.08 for FFR<sub>CT</sub> and -0.07 to 0.06 for FFR. The coefficient of variation of FFR<sub>CT</sub> (CV<sub>FFR<sub>CT</sub></sub>) was 3.4% (95% CI: 1.4%-4.6%) versus 2.7% (95% CI: 1.8%-3.3%) for FFR (CV<sub>FFR</sub>). In vessels with mean FFR ranging between 0.70 and 0.90 (n=25) SD<sub>FFR<sub>CT</sub></sub> was 0.035 and SD<sub>FFR</sub> was 0.043 (p=0.357), whereas CV<sub>FFR<sub>CT</sub></sub> was 3.3% (95% CI: 1.5%-4.3%) and CV<sub>FFR</sub> was 3.6% (95% CI: 2.3%-4.6%).

Conclusions: The reproducibility of both repeated FFR<sub>CT</sub> analyses and repeated FFR measurements is high.

P10.07      Lisbeth Bonde      PERIVASCULAR TISSUE AFFECTS REGULATION OF CORONARY ARTERY TONE

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Background: Diabetic cardiomyopathy is a well-described complication of diabetes characterized by decreased myocardial function. Morphological and metabolic changes in the myocardium have been described but it is unclear whether they are due to direct effects of diabetes on the heart or secondary to changes in coronary artery perfusion.

Aim: To investigate the effect of perivascular tissue (PVT) on regulation of coronary artery tone in a model of diabetic cardiomyopathy.

Method: Male 6-7 weeks old Wistar rats were treated with streptozotocin (STZ; 60 mg/kg) to induce type 1 diabetes. A control group was treated with solvent. After 8 weeks the animals were sacrificed. One segment of the septal coronary artery with PVT and one without were dissected out of each heart and mounted in wire myographs for isometric force recordings. Values are means  $\pm$  SEM.

Results: In coronary arteries from control rats, the maximum contractile response to serotonin decreased from  $2.86 \pm 0.1$  N/m in coronary arteries

without PVT to  $1.49 \pm 0.2$  N/m in arteries with PVT. In STZ-treated rats, the effect of PVT was enhanced: PVT lowered the max response from  $3.06 \pm 0.2$  to  $1.07 \pm 0.1$  N/m.

Conclusion: PVT inhibits serotonin-induced contractility and this effect is more pronounced in hearts from rats with STZ-induced diabetes compared to normal rats. This finding indicates that both normal and dysfunctional myocardium affects the regulation of coronary tone, possibly by release of multiple diffusible factors in a complex interaction.

P10.08      Trine Ørhøj      BIORESORBABLE STENTS FOR TREATMENT OF CORONARY BIFURCATION LESIONS ASSESSED BY OPTICAL COHERENCE TOMOGRAPHY

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Background: Coronary artery disease is often treated by percutaneous coronary intervention (PCI). During PCI a permanent metallic tube called a stent is inserted in the coronary artery to keep the vessel open. Two bioresorbable stents (BRS) are now available for clinical use. BRS degrade in 1-3 years and leave no lifelong foreign body in the coronary vessel. This is believed to improve the long-term safety. Around 15% of patients have a lesion where the vessel divides in two - a bifurcation lesion. We hypothesize that simple treatment of bifurcations using Desolve and Absorb BRS is safe and treatment by Desolve is associated with a lower index of adverse vessel wall features assessed by optical coherence tomography (OCT).

Aim: To compare the 6 months safety and vessel healing after treatment of coronary bifurcation lesions by the Desolve or Absorb BRS.

Methods: Randomization of 120 patients with a simple bifurcation lesion to treatment with either Desolve or Absorb BRS. Treatment will be performed using the provisional stenting approach and OCT is used for stent evaluation before and after BRS implantation. Follow-up OCT at 6 and 24 months. Results will be reported as clinical safety at 6 months (myocardial infarction, revascularization, death) and stent healing index by OCT including malapposition, stent coverage, side branch ostial area late loss, fracture and evaginations.

Perspectives: Systematic data on safety and healing of bioresorbable stents in bifurcation lesions is needed. This is the first randomized comparison of two BRS and the first systematic study on BRS in bifurcation treatment. As a result, this study may improve treatment of bifurcation lesions.

P10.09      Anders Grejs      CARDIAC EFFECTS OF PROLONGED HYPOTHERMIA AFTER CARDIAC ARREST

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Background: In Denmark, 3,500 out-of-hospital cardiac arrests (OHCA) occur every year. Evidence suggests that mild therapeutic hypothermia (TH) improves neurological outcome and survival. Duration, temperature and effects on the heart/circulation remain insufficiently investigated.

Design: This PhD study is a sub-study in a Scandinavian multicenter trial entitled: "TTH48", where resuscitated but still comatose OHCA patients are randomized for 24 versus 48 hours of TH ( $33\pm 1^\circ\text{C}$ ). The PhD study includes patients from Aarhus and Stavanger University Hospitals during a two-year period from Feb 2013 to March 2015. Status: 83 patients included.

Methods and endpoints: This study aims to evaluate the cardiac effects of prolonged TH. Focusing on the cardiac protection and hemodynamics, we divide the PhD study into 3 sub studies:

Study 1: Myocardial protection quantified by blood samples: Troponin T, CK-MB, CoPeptin, NT-proBNP, and MR-proANP. Endpoint: Area under the curve.

Study 2: Echocardiography. By evaluating the longitudinal movement of the mitral annular plan using Tissue Doppler, we indirectly measure salvage of the subendocardial layer. Endpoint: Systolic myocardial velocity during and after TH.

Study 3: Need for inotropes/incidence of arrhythmias in the 24 versus 48 hours group. This sub study has a descriptive character.

Perspectives: OHCA mortality is attributable to neurological damage in 65% of cases. Global ischemia/reperfusion injuries occur in all organs. Describing the potentially cardioprotective effects on the heart is important since post-resuscitation cardiac failure is associated with significant morbidity and decreased quality of life.

P10.10      Peter Skov Jensen      A NEW MODEL FOR STUDYING DIAMETER REGULATION OF PORCINE RETINAL ARTERIOLES AND CAPILLARIES IN VITRO

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Purpose: Disturbances in retinal blood flow secondary to impaired diameter regulation of retinal vessels are involved in the most frequent causes of blindness in the Western World. Therefore, the purpose of the present study was to develop an in vitro technique for studying diameter regulation in both larger and smaller retinal vessels.

Methods: Porcine hemiretinas were mounted in a special tissue chamber developed for studying diameter regulation of vessels with different caliber while controlling temperature, pH and oxygen saturation. The chamber was positioned in a fluorescence microscope, and changes in the diameter of larger arterioles ( $25\ \mu\text{m}$  or larger), pre-capillary arterioles ( $10\text{-}25\ \mu\text{m}$ )

and capillaries (smaller than 10  $\mu\text{m}$ ) were studied after intravascular and extravascular application of the thromboxane analogue U46619 and the glutamate antagonist N-Methyl-D-aspartic acid (NMDA).

Results: In both arterioles, pre-capillary arterioles and capillaries U46619 induced significant contraction after extravascular ( $p < 0.01$ ), but not after intravascular ( $p > 0.20$ ) application. NMDA had no effect on non-precontracted vessels. However in pre-contracted vessels NMDA induced dilatation to a diameter not significantly different from the diameter before contraction in pre-capillaries and capillaries ( $p > 0.52$ ), but not in arterioles ( $p < 0.01$ ).

Conclusions: The thromboxane analogue U46619 contracts both the larger retinal arterioles, pre-capillary arterioles and capillaries after extravascular but not intravascular application. NMDA can restore the diameter of U46619 contracted retinal arterioles and capillaries, but the effect differs between larger and smaller retinal vessels.

P11.01      Maria  
Rasmussen

#### ANOMALIES OF THE KIDNEYS DIAGNOSED BY PRENATAL ULTRASOUND SCREENING AND ASSOCIATED NONURINARY BIRTH DEFECTS: A NATIONWIDE PREVALENCE STUDY

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Background: Prenatally detected kidney anomalies (PDKA) includes cystic kidneys, echogenic kidneys, multicystic kidneys, dysplastic kidneys, kidney agenesis, and horseshoe kidney. Prevalence of PDKA and occurrence of associated nonurinary birth defects need to be monitored to recognize underlying causes, including unknown teratogens.

Methods and material: We aimed to conduct a nationwide prevalence study estimating the prevalence of PDKA at second-trimester and at live birth and the occurrence of associated nonurinary birth defects. Using the nationwide prenatal scanning database, Astraia, we identified fetuses with PDKA between 1<sup>st</sup> of January 2007 and 31<sup>st</sup> of December 2012. An 18-week ultrasound scan was part of the prenatal screening program. A comparison population (1:10) of women attending a second-trimester ultrasound scan matched on calendar year was established using the Danish National Patient Registry. We estimated the prevalence of PDKA at second trimester fetuses and at live birth. Furthermore, we estimated the prevalence of fetuses with nonurinary birth defects at live birth.

Results: We identified 366 fetuses with PDKA at second trimester, 101 (28%) were subsequently either terminated or stillborn. Among live born children with PDKA there was a higher risk of nonurinary birth defects compared to the matched general population.

Conclusion: It is important to differentiate between the prevalence of PDKA

at second trimester and the prevalence at live birth. PDKA may be a predictor of nonurinary birth defects.

P11.02      Anders  
Møllekaer

#### THE ORGANIZATION OF DANISH EMERGENCY DEPARTMENTS

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Background: 21 new emergency departments (EDs) are established at the new acute hospital. The Danish Medical Association estimates that there are 21 different organizational models, which has a negative impact on quality of care. This study investigates differences and similarities in ED organization

Method: The study uses a qualitative design. Five hospitals participated in the study. At each hospital five semi-structured interviews were conducted with hospital management, ED leaders, physicians, nurses and secretaries. The interviews were conducted from October to November 2013.

Results: The five EDs had eight different organizational models. One ED had a functional organizational model. In this model workflow was organized around specialist departments not the patient needs. Doctors from specialist departments primarily performed tasks in their own departments. They were called to the ED on an ad hoc basis. Workflow was uncoordinated, unstructured, unforeseeable and ill defined and with many hand overs. One ED had a process-orientated model. In this model workflow was organized around patient needs across specialist departments. The ED employed most doctors and they only performed task in the ED. A flowmaster and a nurse coordinator were responsible for coordinating and prioritizing patient care. Three ED's had process-orientated model during daytime and a functional model during evening/night time.

Conclusion: The five EDs had in eight different organizational models. ED organization is more complex than estimated. Further research is needed to expand the study to include the remaining Danish ED's and to investigate how different organizational models affect quality of care.

P11.03      Mads Riiskjaer

#### EARLY RISE IN SERUM C-REACTIVE PROTEIN INDICATES SUBSEQUENT SURGICAL COMPLICATION AFTER LOW ANTERIOR RESECTION FOR RECTO-SIGMOID ENDOMETRIOSIS

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Aim: Recto-sigmoid endometriosis is the most advanced and surgically challenging form of the disease. The aim of this study was to demonstrate the potential value of serial measurements of serum C-reactive protein (CRP) and white blood cell count (WBC) after laparoscopic low anterior



resection for endometriosis with bowel involvement.

Background: Recto-sigmoid endometriosis should be treated by the laparoscopic approach, but controversy remains whether to perform shaving or segmental bowel resection. Anastomotic leakage and ureteral injury are feared complications, and early diagnosis is crucial. Measurement of CRP and WBC are used as indicators of such problems in rectal cancer surgery.

Methods: One-hundred-and-five patients who underwent laparoscopic anterior resection for recto-sigmoid endometriosis were monitored daily by serum CRP and white blood cell count (WBC) until discharge from the hospital. Patients with anastomotic leakage or ureteral injury (group A; n=23) were compared to patients without these complications (group B; n=82).

Results: The daily average values of serum CRP were significantly higher in group A starting at the 2nd post-operative day (POD 2,  $p = 0.004$ ). A cut-off value of 60 mg/L on POD 3 resulted in a sensitivity (78%) and specificity (67%) of CRP in assessing the risk of leakage. A decrease in CRP from POD 1 to POD 3 predicted uncomplicated course in 92.0% of the cases. Postoperative WBC values did not display significant differences between the two groups.

Conclusion: An early rise in CRP was a strong indicator of a severe surgical complication. Monitoring of CRP for early detection of anastomotic leakage or ureteral injury is recommended.

P11.04      Mia  
Steengaard  
Olesen

#### THERAPEUTIC ENDOMETRIAL TRAUMA FOR ENHANCEMENT OF EMBRYO IMPLANTATION

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Background: Implantation is decisive for the development of pregnancy, and a key step in assisted reproductive therapy (ART). Despite clinical and scientific advances in fertility treatment, clinical pregnancy rate is still only approx. 30% per transfer. Recent data indicate that therapeutic endometrial trauma (TET) may enhance implantation.

Aim: The aim of this study is to investigate if therapeutic endometrial trauma can improve the clinical pregnancy rate in fertility treatments.

Material and methods: The study is an open randomized 1:1 multicentre clinical trial. In the intervention group, TET is performed with a Pipelle de Cornier at cycle day 18-22 prior to hormonal stimulation. In both groups, blood samples are collected and secretions are aspirated from the uterine cavity at embryo transfer. Samples are frozen for later analysis. Total sample size is 240 patients, and participants were included from February

2014 with 65 subjects so far.

Results: Pending.

Conclusion: This study will provide further data to assess the potential place for TET in public routine in unselected patients in ART, and insight into the possible pathogenic basis of such an effect. Approx. 8-10 % children of a birth cohort are born as a result of fertility treatment in Denmark. If the chance of pregnancy increases with TET, it will not only have great personal significance for the couples, but it will also be of social and financial importance.

P11.05      Gitte Øskov  
                 Skajaa

#### INSULIN SENSITIVITY DURING PREGNANCY AND POST PARTUM

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Aim: The aim of the study is to define insulin requirement during pregnancy and to identify the rapid changes in insulin sensitivity around parturition and the first 6 months post partum. Such knowledge would be clinically useful and markedly improve insulin treatment before and after parturition for women with T1DM and serve to identify the best possible timing of testing women with GDM for the development of T2DM post partum. Furthermore we wish to explore the effects of breastfeeding on glucose tolerance the first year after giving birth in women with T1DM.

Method: Following studies are planned: Insulin resistance throughout pregnancy assessed by insulin requirement in pregnant T1DM women. Retrospective cohort study of women with T1DM with a singleton pregnancy, approximately 600 patients. Hyperinsulinaemic euglycaemic clamp in women before, immediately after delivery and 6 months post partum. We will compare 20 women with GDM in late pregnancy, day 15 post partum and 6 months post partum with 20 normal women investigated at the same time points. Insulin requirement in women with insulin dependent diabetes post partum. Does lactation change insulin sensitivity? Prospective study of the insulin requirement estimated by blood sample (HbA1c) and questionnaire at 1, 3, 6 and 12 months post partum in women with insulin dependent diabetes.

Perspectives: Diabetes is a common condition with important implications for pregnancy outcome and long-term morbidity for mother and offspring. Accordingly, tailoring the best treatment is expected to have beneficial consequences both for the pregnant women and the future generation.

P11.06      Lise Hald  
                 Nielsen

#### ATTENUATED SENSITIVITY OF ALDOSTERONE IN RESPONSE TO DIETARY SALT IN PREECLAMPSIA IS COMPATIBLE WITH ABERRANT ACTIVATION OF ENAC

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**Aim:** During normal pregnancy, the renin-angiotensin-aldosterone system (RAAS) is activated. For unknown reasons, RAAS is suppressed in pre-eclampsia (PE) secondary to proteinuria. We hypothesized that the enzyme plasmin, found in the urine of PE patients, activates the Epithelial Sodium Channel (ENaC) in vitro. Activation of ENaC contributes to increased blood pressure and suppression of RAAS, which implies a reduced reactivity of renin and aldosterone to altered salt intake.

**Methods:** The study is an on-going, randomized, double-blinded, dietary intervention study. Ten PE patients are compared with ten healthy pregnant women. Intervention is a fixed low-sodium diet with addition of either placebo or salt tablets for four + four days achieving high/low sodium intake. Primary outcome is RAAS components. Secondary outcome: Blood pressure and pulsatile index (PI) in the umbilical artery.

**Results:** Mean blood pressure change was  $-3.6\text{mmHg} \pm 1.4$  ( $n=11$ ) in the normal pregnant group and  $1 \pm 7.1\text{mmHg}$ , ( $n=5$ ) in the PE- group (systolic) and  $-0.2\text{mmHg} \pm 1.2$  in the normal pregnant group vs.  $1.6\text{mmHg} \pm 3.9$  in the PE- group (diastolic) in response to low salt intake. In normal pregnancy p-aldosterone increased by  $50.7\text{pg/ml} \pm 4.4$  compared to  $28.7\text{pg/ml} \pm 2.7$  in response to low salt intake. PI index did not change in response to the intervention.

**Discussion:** Blood pressure and PI are unchanged by variations in sodium intake while plasma aldosterone changes in response to salt with higher reactivity in the healthy pregnant group. Data are preliminary.

P11.07 Anne  
Gisselmann  
Egekvist

#### CONSERVATIVE TREATMENT OF RECTOSIGMOID ENDOMETRIOSIS MONITORED BY TRANSVAGINAL ULTRASOUND

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**Background:** Endometriosis is a disease affecting 8-15 % of fertile women and is a cause of abdominal pain and suffering during women's menstrual periods. A subgroup of patients with DIE has an infiltration into the rectosigmoid bowel wall (4-37%). Knowledge of the growth pattern of rectosigmoid lesions related to subjective symptoms is mandatory in order to assess the need for follow-up with transvaginal ultrasound during medical treatment.

**Hypotheses:** When measuring size (twodimensional) and volume (three-dimensional) of rectosigmoid, the measurements are associated with acceptable intra- and inter-observer variation. Symptoms will follow growth of rectosigmoid endometriosis.

**Material and methods:** Two different cohorts of women, based on medical treatment will receive a questionnaire and a transvaginal ultrasound scan (measuring size and volume) at inclusion, (6) and 12 months later.

**Perspectives:** Patients treated conservatively may be followed by questionnaires, thereby reducing the need for time consuming clinical

controls.

P11.08      Martin Christensen      PREECLAMPSIA AND ARTERIAL STIFFNESS - A 10-YEAR FOLLOW-UP OF PREVIOUSLY PREECLAMPTIC WOMEN

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Introduction: Several studies show an association between preeclampsia and premature development of cardiovascular disease (CVD). The association is incompletely understood, but probably includes pre-existing common risk factors. However, preeclampsia may also induce permanent vascular and metabolic alterations that could affect systemic arterial elastic properties. In this regard, arterial stiffening could represent a link between the systemic effects of preeclampsia and CVD risk.

Objectives: We aimed to evaluate the effect of preeclampsia on arterial stiffness markers in women with a history of preeclampsia.

Methods: A 10-year follow-up study comparing 21 exposed women (previous pre-eclamptic pregnancies) and 21 unexposed women (previous normotensive pregnancies) matched on age and time since delivery. The two groups were compared with respect to markers of arterial stiffness and traditional CVD risk factors.

Results: Our analysis showed a higher aortic pulse wave velocity in women with a history of preeclampsia than in unexposed women ( $8.04 \pm 1.47$  vs.  $7.29 \pm 0.87$  m/s, respectively,  $P=0.057$ ). However, the difference fell marginally short of statistical significance. Waist-Hip ratio ( $P<0.05$ ) and percentage using anti-hypertensive drugs ( $P=0.02$ ) were significantly higher in previously preeclamptic women.

Conclusion: Women with preeclamptic pregnancies 10 years earlier tended to have higher pulse wave velocity than women with previous normotensive pregnancies. To the best of our knowledge, this is the first comparative assessment of arterial stiffness 10 years after pregnancies complicated by preeclampsia. More results will be presented at the 2015 PhD day.

P11.09      Lise Haaber Thomsen      THE USE OF PREIMPLANTATION FACTOR (PIF) IN OPTIMIZING EMBRYO SELECTION IN IVF TREATMENT - A DESCRIPTIVE COHORT STUDY IN FOUR DANISH IVF CLINICS

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**Introduction:** Preimplantation Factor (PIF) is a pregnancy-specific peptide secreted only by viable embryos. PIF can be detected in embryo culture media prior to embryo transfer (ET) and in maternal circulation as early as four days after ET. PIF plays an essential role in preparing the local uterine environment for implantation by modulating maternal immune response, promoting embryo-decidual adhesion and regulating adaptive apoptotic processes involved in implantation. PIF production by the embryo is presumed to be an indicator of high embryo quality, and future routine PIF analysis of the embryo culture media might contribute positively to a more accurate detection of the most viable embryo selected for transfer. Pilot studies have demonstrated that PIF negative embryos fail to implant, but a large prospective study is required to determine the possible role of PIF analysis as an additional non-invasive tool in IVF embryo selection.

**Methods:** Patients (n=900) will be enrolled from four IVF-clinics from May 2014 to May 2016. Following embryo transfer, embryo culture media will be collected and frozen for later concurrent evaluation of PIF levels by immunoassay. Biochemical pregnancy is assessed by serum hCG 14 days following oocyte pick-up. Implantation and clinical pregnancy are evaluated by ultrasound examination in gestational week 7. Live birth rates will be recorded after delivery.

**Results:** The primary outcome measures of the study are PIF status of the embryo and live birth. Secondary outcome measures are biochemical pregnancy, implantation and clinical pregnancy rates in patients with PIF positive and PIF negative embryos, respectively.

P11.10      Rune Dall  
                 Jensen

#### DREAM TEAM - A PREGRADUATE SURGICAL TALENT DEVELOPMENT PROJECT

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**Background:** Talent identification and the development of expertise is a well-established research area, primarily focusing on development of individual skills. However, research call for more attention to social and institutional foundations of talent identification and the development of expertise. Dream Team is a pregraduate surgical talent development program at Aarhus University Hospital. It aims to identify and develop surgical talents already at a pregraduate level. The program consists of 5 days bootcamp followed by 4 months mentorship for the 8 best students from the bootcamp.

**Aims:** The PhD project aims to produce new relevant and necessary knowledge regarding pre-graduate surgical talent development; to refine and develop the Dream Team program activities, and to produce a solid, research based design for pre-graduate surgical talent development, which can be used as a starting point for future pre-graduate talent

development within other specialties.

Methods: The project includes 4 sub-projects: 1. Dream Team - What is the current status? 2. Strategies for surgical talent development - How do we find the talents? 3. The cultivating effect of the talent development context - How do we make the talents as good as possible? 4. Design of a curriculum within Danish medical education - How can we make talent development across all specialities? The PhD project is based on qualitative research methods. The theoretical framework is based on theories regarding development of expertise, learning in communities of practice and the sociological concepts of Pierre Bourdieu. Furthermore, the project will include practical knowledge collected in the elite sports sphere.

P12.01      Susanne Haas      ALTERED CORTICAL PROCESSING IN RESPONSE TO RECTAL AND ANAL STIMULI IN PATIENTS SUFFERING FROM IDIOPATHIC FECAL INCONTINENCE

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Background: Rectal and anal canal intact sensory function is essential for satisfactory continence. Thus, we hypothesized that patients with idiopathic fecal incontinence (IFI) possess abnormal sensory pathways of the brain-gut axis, which would be reflected in cortical evoked potentials (CEP) following mechanical stimulation of the rectum and anal canal.

Method: 19 healthy women (age: 56±11, Wexner score: 1.1±1.3) and 19 women suffering from IFI (age: 60±14, Wexner score: 14.7±2.9) underwent repeated rapid balloon distensions of the rectum and anal canal at sensory level of unpleasantness/ urge to defecate whilst recording CEPs. Latencies, amplitudes and topographical distribution from rectally elicited CEPs and topographical analysis were compared between the groups. Furthermore, rectal and anal data was also analysed using single sweep spectral band analysis determining the relative amplitude of the five spectral bands.

Results: IFI patients had increased spectral content in rectal delta and theta bands which was also reflected in prolonged CEP latencies. Amplitudes and topographical distribution were similar between IFI patients and controls. The spectral content of the CEPs elicited in the anal canal showed significant increase in the delta and gamma band, as well as a decrease in the alpha and beta band when compared to controls.

Conclusion: IFI is associated with impaired visceral sensation in combination with altered cortical processing in response to both rectal and anal stimuli. These findings support the hypothesis that afferent dysfunction on both cortical and sub-cortical levels are important factors in the pathogenesis of functional gastrointestinal disorders.

- P12.02      Anders Mark Christensen      ROBOT-ASSISTED ILEOANAL ANASTOMOSIS - COMPARISON OF EARLY OUTCOME WITH CONVENTIONAL LAPAROSCOPY
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- Background: Robot-assisted laparoscopy is becoming the preferred technical approach for many colorectal procedures, although evidence for its efficacy over conventional laparoscopy is scarce.
- Method: We collected data on intraoperative and early postoperative outcome following ileoanal anastomosis procedures performed by either a conventional laparoscopic approach (CL) or with ancillary robot-assistance (RA). The two procedures were compared on uni- and multivariate regression analyses, adjusting for potential baseline confounders.
- Results: During the period November 2010 - March 2014, twenty-five CL and seventy RA procedures were performed. The mean duration of operation was 221 min (95% CI: 192;249) for CL and 286 min for RA (95% CI: 270;301). Two (8%) CL procedures and 8 (11%) RA procedures were converted to open surgery. Minor and major complications occurred for 11 (44%) and 2 (8%) patients from the CL group and for 26 (37%) and 16 (23%) patients from the RA group; these differences were not statistically significant. Postoperative admission length was 9.1 days (95% CI: 7;11) in the CL group compared to 8.9 days (95% CI: 7;10) in the RA group. The difference (0.23 days (95% CI: -2.1;2.6) was not significant. Reoperation and readmission rates were similar. On multivariate regression analyses, only duration of operation was significantly different between CL and RA (73 minutes (95% CI: 36;111).
- Conclusion: Besides a longer duration of operation for RA procedures, no differences between CL and RA in terms of early postoperative outcomes following ileoanal anastomosis were demonstrated. Results from ongoing randomized controlled trials are greatly anticipated.
- 
- P12.03      Michelle Meier      THE PROTEOMIC RESPONSE TO LIVER INJURY AND REGENERATION - AN EXPERIMENTAL RAT STUDY
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- Background: The liver is unique in its ability to repair itself. The regenerative capacity makes it possible to remove large portions of liver without impairment of liver function. Partial hepatectomy (PH) represents first line

treatment for primary and secondary liver malignancies. PH leaves remaining tissue undamaged and the remaining liver cells have the ability to proliferate and restore lost liver mass. The regenerative potential is however limited. The upper limit for single PH is approximately 70% in humans and 95% in rats above which, regeneration fails leading to liver failure. PH of 30% or less causes a delayed and asynchronous regenerative process in rat liver. Liver regeneration is a complex mechanism of biochemical signal pathways. The numbers of proteins expressed do not correlate with the coding potential of the organism. Hence, it is necessary to determine the protein expression levels directly and not indirectly through mRNA. This can be done by proteomic analysis.

**Aim:** The aim of this study is to identify proteomic changes and up/down regulations in protein pathways involved in liver regeneration after liver injury.

**Methodology:** An experimental rat study. 30% (n=24), 70% (n=24) and 90% (n=24) PH is performed together with a SHAM group (n=24) undergoing laparotomy without PH. The rats are euthanized at day 1 (n=8), 3 (n=8) and 5 (n=8). Liver tissue and blood are sampled. Proteomic, stereological and liver specific serological analyses will be conducted.

**Results:** The surgical part of the study has been finished with inclusion of liver tissue and blood from 96 animals. The proteomic, stereological and serological analyses are in progress.

- P12.04      Kirstine Petrea      MANAGEMENT OF PATIENTS WITH HEPATOCELLULAR CARCINOMA:  
Bak-Fredslund      CLINICAL IMPACT OF  $^{18}\text{F}$ -FDGGAL PET/CT MOLECULAR IMAGING WITH  
LABELLED GALACTOSE TRACER  $^{18}\text{F}$ FDGAL

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**Background:** The non-invasive diagnosis of hepatocellular carcinoma (HCC) is often troublesome. Diagnosis of HCC today is based on morphological changes, primarily contrast enhanced CT(cCT), which can demonstrate changes in blood perfusion in tumour tissue. If a suspicious liver nodule does not exhibit typical HCC features on cCT, an additional imaging modality - US or MRI - is applied. For early HCC, the sensitivity of these diagnostic criteria is, however, only around 30%. Positron emissions tomography (PET) can demonstrate early biochemical changes and the galactose tracer analogue  $^{18}\text{F}$ -FDGal is used for PET/CT measurements of regional metabolic capacity of the liver. Preliminary data indicate that  $^{18}\text{F}$ -FDGal PET/CT may be sensitive for diagnosis of HCC, because malignant hepatocytes have different metabolic rates of  $^{18}\text{F}$ -FDGal compared with surrounding non-malignant cells. Preliminary clinical use of  $^{18}\text{F}$ -FDGal PET/CT in 40 patients supports this.

**Aim:** We wish to test prospectively the hypothesis that  $^{18}\text{F}$ -FDGal PET/CT significantly improve diagnostic evaluation and therapeutic monitoring of



patients with HCC when used supplementary to conventional cCT, US, MR, and biopsy.

Methods: Patients referred to Aarhus University Hospital for treatment of HCC are included. They will undergo cCT and  $^{18}\text{F}$ -FDG PET/CT with the images analysed blinded for each other. The Multidisciplinary Liver Tumour Board decides therapeutic strategies based on standard assessment, first without  $^{18}\text{F}$ -FDG PET/CT and then with  $^{18}\text{F}$ -FDG PET/CT, being compared for clinical impact. 40 of the patients will also undergo  $^{18}\text{F}$ -FDG PET/CT 1-3 months after treatment to evaluate its use in therapeutic monitoring.

P12.05      Casper Larsen    STRUCTURAL AND FUNCTIONAL STUDIES OF COBALAMIN UPTAKE AND TRANSPORT

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Vitamin B<sub>12</sub> (Cobalamin, Cbl) plays a key role in the human metabolism and deficiency can lead to anemia and neurological disorders. Humans must obtain the compound through dietary sources and have evolved an elaborate absorption- and transport pathway from the food to the body's cells. Cbl uptake in non-epithelial tissues occurs via the endocytic receptor CD320 that recognizes the compound in complex with the carrier protein transcobalamin (TC). CD320 belongs to the low-density lipoprotein (LDL) receptor family, as it possesses two extracellular LDL-receptor type A repeats. These repeats are small domains harboring a Ca<sup>2+</sup>-binding site, which is crucial for ligand interaction. A general mechanism for ligand recognition by receptors of the LDL family has been presented, which involves the attraction of basic residues from the ligand by acidic, Ca<sup>2+</sup>-coordinating residues in the receptor-domains. As uptake of TC-Cbl is Ca<sup>2+</sup>-dependent, it is likely that interaction with CD320 occurs in a similar manner.

The focus of this PhD study is to obtain further knowledge of cellular Cbl uptake by providing a detailed characterization of the interaction between CD320 and TC-Cbl. The main objective will be to determine the crystal structure of the complex. So far, initial crystallization experiments have shown promising outcomes for future optimization. Preliminary mutagenesis and binding studies have also been performed and support the proposed binding model.

By elucidating these structural and functional characteristics, a more complete understanding of Cbl uptake and transport is achieved. Hence, better strategies for treatment and prevention of Cbl deficiency can be developed.

P12.06      Linda Skibsted    MILK IS AN EXCELLENT SOURCE FOR VITAMIN B12. AN EXPERIMENTAL  
Kornerup                STUDY IN A RAT MODEL

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Background: In general, food-bound vitamin B12 (B12) has a poor bioavailability. Curiously, some studies indicate that B12 present in milk is absorbed even more efficiently than free B12.

Objective: To explore the uptake of free B12, B12 bound to milk protein (recombinant transcobalamin (rTC)) and B12 in milk.

Methods: Radioactive B12 ( $^{57}\text{Co}$ -B12), either free or bound to rTC, was administered by gastric gavage to two groups of 15 rats. Five rats from each group were sacrificed after 2, 24, and 48 hours. Likewise, groups of rats ( $n=10$ ) were fed with  $^{57}\text{Co}$ -B12 in its free form, present in milk, or bound to rTC added to milk and sacrificed 24 hours later. Weight quantities of tissue were homogenized, and  $^{57}\text{Co}$ -B12 was measured employing a gammacounter. All results were expressed as percentage of given dose per organ.

Results: After feeding with free B12, the highest percentage at 2, (24) and [48] hours expressed as median and (range) was recovered in the kidney: 0.061% (0.052-0.075); (14% (10-17)) and [18% (13-20)] followed by the small intestine: 3.9% (2.0-5.6); (1.8% (1.1-2.2)) and [1.2% (0.8-1.9)] and liver: 0.056% (0.017-0.090), (1.1% (0.70-1.6)) and [1.1% (0.68-1.2)]. No significant difference was observed between the uptake of free B12 and B12 bound to rTC or present in milk.

Conclusion: We document that B12 present in milk is absorbed as efficiently as is free vitamin B12. Our results confirm milk as an excellent source for vitamin B12, but does not support that milk is a better source than free vitamin B12. We plan to do further rat studies on the topic in the nearest future.

P12.07      Emilie Glavind      ALCOHOLIC HEPATITIS MARKEDLY DECREASES THE CAPACITY FOR UREA SYNTHESIS

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Background: Urea synthesis is an essential metabolic liver function that serves a key regulatory role in nitrogen (N) homeostasis. The capacity for urea synthesis decreases in patients with compromised liver function. In contrast, it increases in patients with inflammation. Alcoholic hepatitis (AH) involves both mechanisms, but it is unknown how their effects on urea synthesis are balanced.

Aim: To investigate how AH affects urea synthesis.

Methods: We included 20 patients with AH. Eleven had severe AH: a

Glasgow alcoholic hepatitis score (GAHS)  $\geq 9$ . The capacity for urea synthesis was quantified by the Functional Hepatic Nitrogen Clearance (FHNC), i.e. the slope of the linear relation between urea-N synthesis rate and blood  $\alpha$ -amino-N concentration during alanine infusion. The FHNC was related to another metabolic liver function, the Galactose Elimination Capacity (GEC), and to clinical liver status assessed by the Model for End-Stage Liver Disease (MELD) score.

Results: FHNC was markedly decreased to  $7.2 \pm 4.9$  l/h (mean  $\pm$  SD) in the patients (normal range 20-35 l/h) and most so in those with severe AH ( $4.9 \pm 3.6$  l/h vs.  $9.9 \pm 4.9$  l/h,  $P < 0.05$ ). The GEC was less markedly reduced than the FHNC and they were dissociated. There was an inverse relation between the FHNC and MELD score ( $r^2 = 0.27$ ,  $P < 0.05$ ).

Conclusions: AH markedly decreases the capacity for urea synthesis and to a level previously only measured in acute liver failure. In AH, thus, the metabolic failure prevails so that the liver cannot appropriately deliver the metabolic up-regulation found in other stressful states including inflammation. This may contribute towards the frail prognosis of the patients.

P12.08      Nikolaj Worm      HEPATIC TRANSPORT OF CONJUGATED BILE ACIDS IN HUMANS  
Ørntoft      QUANTIFIED BY  $^{11}\text{C}$ -CHOLYLSARCOSINE PET/CT

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Introduction: Hepatobiliary secretion of bile acids is an essential liver function, not accessible by conventional means of measurements. We examined whether PET/CT using the radiolabeled bile acid [N-methyl- $^{11}\text{C}$ ]cholylsarcosine ( $^{11}\text{C}$ -CSar) as tracer allowed quantitative assessment of this function.

Methods: 10 healthy subjects and 10 patients with varying degrees of cholestasis underwent two 60 minutes dynamic PET/CT recordings with intravenous administration of  $^{11}\text{C}$ -CSar. Blood concentrations of  $^{11}\text{C}$ -CSar were measured in a radial artery and a hepatic vein, while PET recorded the concentration in the liver tissue and the common hepatic duct. Fractional secretion (FS) at a given time point was calculated as the ratio between  $^{11}\text{C}$ -CSar secreted into bile and  $^{11}\text{C}$ -CSar supplied to the liver by the blood.

Results: The hepatic extraction from blood was about 90% (range 85 - 94%) throughout the PET recordings in healthy subjects, while in the patients it decreased with time from initially 86% (77-93%;  $p = 0.09$ ) to 50% (28 - 59%;  $p < 0.0001$ ). This demonstrates a normal hepatic uptake of  $^{11}\text{C}$ -CSar, combined with significant backflux to blood in patients with cholestasis, and essentially no backflux in healthy subjects. Median FS ( $t = 50$  min) was 73% (55 - 80%) in healthy subjects and 38% (17 - 70%) in patients with cholestasis ( $p < 0.001$ ). This demonstrates reduced secretion of  $^{11}\text{C}$ -CSar from liver to bile in patients with cholestasis.

Conclusions:  $^{11}\text{C}$ -CSar PET/CT enables quantification of hepatobiliary secretion of conjugated bile acids. In patients with cholestasis, hepatic uptake of  $^{11}\text{C}$ -CSar was normal, while there was backflux of  $^{11}\text{C}$ -CSar to blood and a reduced secretion from liver to bile.

P12.09 Anne Grosen INFLUENCE OF AZATHIOPRINE TREATMENT ON SEMEN QUALITY IN MEN WITH INFLAMMATORY BOWEL DISEASE

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Background: Fertility is a major concern among patients with inflammatory bowel disease (IBD). Fear of teratogenicity of the anti-inflammatory treatment may lead to discontinuation of medication and poor disease control. Studies on the effect of azathioprine (AZA) on semen quality and pregnancy outcomes have been contradicting. Since AZA interferes with nucleic acid synthesis, treatment can theoretically produce germ cell mutations as well as teratogenic effects.

Aim: To investigate the influence of AZA treatment on semen quality in patients with IBD.

Hypotheses: Basic semen analysis is inadequate to determine damage to spermatozoa from AZA treatment. AZA incorporation in sperm DNA is detectable and leads to increased rates of strand breaks. Increased rates of sperm DNA strand breaks induced by AZA are reversible.

Methods: 30 IBD patients treated with AZA in clinical and biochemical remission. 10 IBD patients before start or tapering of AZA treatment. 40 healthy controls. Participants deliver a semen and blood sample. Patients with change in AZA treatment deliver a new sample after initiation/tapering of the drug. Standard sperm analysis according to WHO 2010; sperm cell DNA fragmentation measured by the sperm chromatin structure assay using flow cytometry; DNA-TGN content in sperm DNA measured by chromatografi.

Perspectives: Male IBD patients and their spouses often request information on the effect of medication on male fertility. Fears and doubts significantly affect family planning. By gaining new insight, we hope to be able to advise our patients in the future and improve adherence to the treatment.

P12.10 Lea Ladegaard ORAL HEALTH STATUS OF PATIENTS WITH LIVER CIRRHOSIS  
Grønkjær

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## Hospital

Background: Liver cirrhosis is associated with a lifestyle that contributes to oral neglect and untreated oral diseases, which can affect general health and oral health-related quality of life (OHRQOL).

Objective: To describe the oral care habits and self-perceived oral health in patients with liver cirrhosis, as well as to evaluate the OHRQOL.

Methods: From Oktober 2012 to May 2013 a prospective study was conducted. OHRQOL was measured using the 14-item Oral Health Impact Profile questionnaire (OHIP-14), and participants answered questions on oral care habits and perceived oral health. Findings were compared with the survey on Danish population's dental status and oral health from 2012, including material from 4.240 citizens.

Results: A total of 107 participated. The oral care habits and self-perceived oral health of cirrhotic patients was poorer than the Danish population; cirrhosis patients had fewer teeth ( $p=0.0001$ ), problems with oral dryness ( $p=0.0001$ ), attended the dentist less frequent ( $p=0.001$ ), and brushed rarer teeth ( $p=0.001$ ). The mean OHIP-score was  $5.21 \pm 7.2$  and the most commonly reported oral health impacts were related to taste and nutrition. An association was seen between the total OHIP-score and the nutritional risk score ( $p=0.01$ ).

Conclusion: For the first time, OHRQOL was measured in patients with liver cirrhosis. Results indicated a low impact of life, but attitude toward oral health and hygiene were weak among cirrhotic patients. Awareness of potential associations between liver cirrhosis, oral health and general quality of life needs to be increased in cirrhotic patients and clinicians.

P13.01      Sigr d Bjerger      NON-SURGICAL COMPLICATIONS AND CHANGES IN QUALITY OF LIFE  
Gribsholt      AFTER GASTRIC BYPASS SURGERY

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Background: Roux-en-Y gastric Bypass (RYGB) results in pronounced weight-loss in severely obese people but may be associated with various complications. Many non-surgical complications are overlooked and un-registered. Self-reported data on this issue are sparse; whether gender differences exist is not fully elucidated.

Aim: In a population-based cohort of RYGB patients, we aim to estimate prevalence of non-surgical complications, explore quality of life (QoL), and whether gender differences exist.

Design: A questionnaire containing questions on complications and validated symptom scores on hypoglycaemia, dumping, and QoL (SF-12) was mailed spring 2014 to all RYGB-patients in the Central Denmark Region 2006-2011. We tabulated by gender, by Poisson regression, and

calculated risk ratios of complications comparing gender.

Results: The response-rate was 64% (1429/2242), 80% were females. Mean BMI reduction was 41%, 73% experienced one or more complication, most commonly fatigue (48%), followed by abdominal pain (42%), diarrhea (34%), and anaemia (29%). A higher risk of gallstones (Incidence Rate Ratio (IRR) 2.9, 95% confidence interval(1.7;4.9)), anaemia (IRR: 2.1 (1.6,2.8)), fatigue (IRR: 1.5 (1.2;1.7)), and dumping syndrome (IRR: 1.4 (1.0,1.9)) and a lower risk of kidney stones (IRR: 0.7, (0.4;1.0)) was observed among females compared with males. No gender differences were found concerning QoL (8% reported worse wellbeing, 85% better or much better), or scores from SF-12.

Conclusion: 73% of the operated experienced non-surgical complications. Complications differed by gender and were most common among females. The majority (85%) reported improved QoL with no gender-specific differences.

P13.02      Max Norman      THE EFFECTS AND MECHANISMS OF BIOAVAILABLE RED CLOVER  
                 Tandrup      ISOFLAVONES ON MENOPAUSAL SYMPTOMS AND BONE RESORPTION  
                 Lambert

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Background: Isoflavones with estrogenic capabilities have been shown to exert beneficial effects on the symptoms of menopause and bone mineral resorption.

Aim: To test the effects of a highly bioavailable and aglycone rich isoflavone formulation derived from Red Clover (RC) on existing menopausal symptoms & associated diseases.

Methods: 60 post-menopausal women with existing symptoms of menopause (> 5 hot flushes/day), mean age of 52.5 yrs and mean follicle stimulating hormone of 72.4 were randomly assigned either a daily dose of RC extract comprised of 33.7 mg/d of isoflavone aglycones or placebo formula for 12 weeks. Change in hot flush frequency (HFF) and hot flush intensity (HFI) from baseline was measured by 24-hour skin conductance (SC) on the arm at the ante brachia at weeks 0, 6 and 12. Bone mineral density (BMD) was assessed by DEXA at weeks 0 and 12.

Results: No change in either HFF or HFI was found within the placebo group. A significant reduction in HFI from baseline was found within the RC group (P <0.05), equating to a mean of -32.1%, along with a significant (P <0.05) decrease in HFF within the RC treated group equating to a mean -15.4%. There was a significant (P <0.05) fall in BMD within the placebo group at the femoral neck and the columna lumbalis regions, the RC group also had a significant (P <0.05) decrease in femoral BMD. There was no significant change from baseline to week 12 in BMD at columna lumbalis

region in the RC group.

Conclusion: Highly bioavailable RC derived isoflavones can reduce symptoms of the menopause and can attenuate estrogen dependent bone mineral resorption. SCs are useful tools for capturing objective physiological data for hot flushes.

- P13.03      Sofie Hertz  
                 Rønn      TREATMENT WITH VITAMIN K2: A RANDOMIZED CONTROLLED CLINICAL TRIAL, INVESTIGATING THE EFFECT ON BONE METABOLISM, INSULIN SENSITIVITY AND ARTERIAL STIFFNESS

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Background: Osteoporosis, diabetes, metabolic syndrome and cardiovascular disease are common diseases in the Western world. Several evidence based treatments are available for the treatment of osteoporosis but since the condition is common prevention of osteoporosis is important. Osteocalcin (OC) is the major noncollagenous protein produced by the osteoblast. The exact role of OC is not clear; it most likely functions as a regulator of bone mineral maturation. Vitamin K is a co-factor in the carboxylation of osteocalcin.

Research hypotheses: Vitamin K2 (MK-7) reduces undercarboxylated osteocalcin in postmenopausal women and reduces bone turnover and increases bone mineral density; increases insulin sensitivity and decreases indices of arterial calcification.

Methods: The trial is a randomized double blinded controlled clinical trial. 150 postmenopausal women with osteopenia are randomized to vitamin K2 375 µg per os per day or placebo for 12 months. Bone turnover is assessed by biochemical markers, bone mineral density, assessed by DXA- and HRpQCT-scans, insulin sensitivity, assessed by HOMA test, and indices of arterial calcification, assessed by pulse wave velocity.

Perspectives: The study will provide new knowledge about the possible effects of vitamin K2 on bone and glucose metabolism as well as on arterial calcification. Positive effects of vitamin K2 on one or more of the investigated endpoints would provide significant impact on the possibilities for preventing osteoporosis, diabetes, metabolic syndrome and heart diseases at the population level.

- P13.04      Ann  
                 Bjørnshave      DOSE-RESPONSE EFFECT OF WHEY PROTEIN CONSUMED AS PRE-MEAL ON POSTPRANDIAL LIPEMIA IN PERSONS WITH THE METABOLIC SYNDROME

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Introduction: Postprandial triglyceridemia (PPL) is an independent risk factor for cardiovascular disease (CVD). Reduction of increased PPL, as a part of CVD prevention, is hence pivotal in especially subjects with increased risk of CVD e.g. with metabolic syndrome (MeS) and type 2 diabetes (T2D). Whey protein (WP) consumed as pre-meal triggers a prominent increase in the early postprandial insulin response. At present no studies have examined, if a pre-meal of protein influences the subsequent PPL of a meal.

Objective: To examine whether the triglyceride (TG) and ApoB-48 responses are affected by a dose-response effect of WP consumed as a pre-meal prior to a fat-rich meal in MeS subjects. Secondly we will look at plasma responses of insulin, glucose, glucagon and free fatty acids (FFA).

Methods: Twenty subjects with MeS completed the acute, randomized, cross-over study with three arms. Each test day was initiated with collection of fasting data (blood, urine, anthropometric measurements and visual analogue scale (VAS)). A pre-meal of 0, 10 or 20 g WP was served 15 min prior to a standardised, fat-rich breakfast (second meal). Blood samples were drawn for 360 min. Urine was collected as pooled samples. VAS was fulfilled every 30 min in the postprandial period after second meal.

Results: Preliminary results showed that plasma insulin concentration was significant higher after 10 and 20 g WP compared to 0 g in the pre-meal ( $P < 0.001$ ) to time 0 and 15 min. Blood glucose concentration was significant lower after 20 g WP compared to 0 g WP ( $P < 0.05$ ) to time 30 min. The responses of glucagon remain unchanged among the three groups. Analysis of TG, ApoB48 and FFA will follow.

- P13.05      Morten Høgild      SUBSTRATE METABOLISM, GROWTH HORMONE (GH) SIGNALING, AND  
Pedersen      INSULIN SENSITIVITY DURING FASTING IN LEAN AND OBESE HUMAN  
SUBJECTS AND THE IMPACT OF GROWTH HORMONE RECEPTOR (GHR)  
BLOCKADE

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Background: Calorie restriction increases longevity in many species and attenuate the development of chronic disorders including type 2 diabetes, cardiovascular diseases and cancer. In mice reduced activity of insulin-like growth factor I (IGF-I) and/or insulin is associated with extended longevity. GH is the main regulator of IGF-I production, but the molecular mechanism whereby GH switches from IGF-I stimulation (protein anabolism) to fatty acid oxidation as well as induction of insulin resistance during fasting remains enigmatic.

Hypotheses: The changes of the global metabolome, induction of insulin resistance, and the shift in metabolism from protein anabolism to lipolysis



together with the potentially favorable effect of calorie restriction during fasting depend on preserved fasting-induced GH secretion.

Primary endpoints: 1) GH signaling in vivo in the absence and presence of GHR blockade, 2) Substrate metabolism and insulin sensitivity and 3) Metabolomics

Aim: We wish to provide knowledge on changes in metabolites and shift in signaling pathways that take place at the transition to the fasting state among lean and obese subjects. Furthermore we wish to determine the effect of GH on the adaption of the metabolism to a fasting state.

Methods: Ten healthy subjects will be studied on 3 occasions: 1) After an overnight fast, 2) After 72 hours of fasting, 3) After 72 hours of fasting and concomitant GHR blockade. Each study consists of a 4 h basal period followed by a 2 h euglycemic, hyperinsulinemic clamp. Blood samples together with muscle and fat biopsies are obtained throughout the study day.

Results: The study is in progress and is expected to be completed in 6 months.

P13.06      Peter Breining      EFFECTS OF HYPERTHYROIDISM ON AMOUNT AND ACTIVITY OF BROWN ADIPOSE TISSUE

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Background: Within the last decade focus on the benefits of brown adipose tissue (BAT) has greatly increased due to the discovery of active BAT in man. The large majority of knowledge on BAT is derived from studies on rodents and very little is known about the amount and effect on the metabolism in humans. In rodents thyroid hormones are known to increase amount and activity in BAT but two studies in humans published within the last year reach contradictory conclusions. The aim of this study is to investigate the effects of thyroid hormones on the amount and activity of BAT.

Aim: To study the effects of thyroid hormones on BAT in humans

Methods: 10 hyperthyroid subjects are to be examined. They are all newly diagnosed and untreated patients over the age of 50. All are to be scanned for active BAT by the integrated (18) F-fluorodeoxyglucose ((18) F-FDG) positron-emission tomography and computed tomography (PET-CT) before and 3-6 months after treatment. To activate BAT all subjects are cooled with a bag of crushed ice placed under their feet in intervals to avoid shivering. Indirect calorimetry is done to determine the basal metabolic rate and subcutaneous fat biopsy to examine the effect on subcutaneous fat.

Preliminary results: Active BAT has been detected in one out of three middle aged women.

Conclusions: Results from rodent studies cannot be directly transferred to humans. BAT is scarce and the amount varies greatly between individuals. So far, no conclusions can be made from this study.

P13.07      Tanni Kjær  
                 Borgbo      SIZE MATTERS: THE EFFECTS OF THE ANDROGEN RECEPTOR CAG REPEAT LENGTH ON HUMAN ANTRAL FOLLICLE FUNCTION.

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Introduction: The transcriptional domain of the androgen receptor (AR) contains a polymorphic CAG repeat sequence, which have been correlated to the transcriptional activity of AR. In women, the AR ligands are the androgens testosterone and androstenedione, which are produced in the ovarian follicles. This study investigates the effects of the AR CAG repeat length, by evaluating the hormone and gene expression profiles of human small antral follicles.

Material and methods: In total, 169 human small antral follicles from 53 women were included in this study. The intrafollicular hormone content of 163 follicle fluid samples and gene expression levels of 40 granulosa cell samples were correlated to the CAG repeat length, evaluating the following parameters: follicle diameter, intrafollicular levels of Anti-Müllerian Hormone (AMH), progesterone, oestradiol, testosterone and androstenedione, and granulosa cell gene expression levels of FSHR, LHCGH, AR, CYP19A1, and AMH.

Results: Long CAG repeat lengths in AR (23-26 mean CAG repeats) was associated with significantly decreased testosterone levels as compared to medium CAG repeat lengths (20.5-22.5, P=0,007) and small CAG repeat lengths (17.5-20.5, P=0,007). In follicles ranging from 3-6 mm in diameter, the long CAG repeats was associated with significantly increased LHCGR gene expression levels compared to small CAG repeat lengths (P=0,008), and borderline significant compared to medium CAG repeat lengths (P=0,06).

Conclusion: Long CAG repeat lengths in AR (23-26 mean CAG repeats) significantly influenced the function of human small antral follicles.

P13.08      Lise Bols  
                 Andersen      CHARACTERIZATION OF THE CLINICAL AND MOLECULAR EFFECTS OF A NOVEL AVP SIGNAL PEPTIDE MUTATION

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Variations in the arginine vasopressin (AVP) gene cause familial neurohypophyseal diabetes insipidus (FNDI) presumably because variant AVP prohormone is retained in the magnocellular neurons in the hypothalamus leading to neuronal cell death. One reason for retaining the hormone may be incomplete cleavage of the signal peptide.

The first aim was to characterize the clinical phenotype of autosomal dominant FNDI in a Danish family. The second aim was to compare the cellular effects with those of other variations found in the signal peptide through heterologous expression in SH-SY5Y cells.

A thirst deprivation test was performed to determine whether the clinical phenotype was complete or partial. Using mass spectrometry, we determined whether the AVP signal peptide in different variations was cleaved correctly compared with the wild type hormone. The fate of the variant AVP prohormone will be further investigated by means of confocal laser scanning microscopy of transiently transfected cells. Furthermore, using qPCR, we examined whether wild type and variant AVP variants were expressed to the same extent.

The thirst deprivation test revealed an almost complete phenotype with small capacity to secrete biological AVP. Mass spectrometry showed an incomplete cleavage of the signal peptide in the investigated variants, which probably leads to intracellular hormone retention. We expect to be able to show intracellular localization by staining transfected cells. A subsequent viability test will examine how the transfected cells react to a stressful condition like heat shock and to which extent the variant cells' viability is diminished compared with that of the wild type cells.

P14.01      Mark Klitgaard      RESVERATROL AMELIORATES LIPOPOLYSACCHARIDE-INDUCED INSULIN  
Nøhr                              RESISTANCE IN MICE

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Background: In addition to obesity, a chronic low-grade inflammation is often seen believed to responsible for the induction insulin resistance and ultimately a key component in the development of diabetes. The triggering factor of this low-grade inflammation is largely unknown but several hypotheses have been suggested. Endotoxemia by gut-barrier penetration of lipopolysaccharides (LPS) from the gut microbiota has been suggested as one triggering factor for this inflammatory state. Resveratrol (RSV) is a

potential anti-diabetic compound found in especially red grapes and has previously shown promising effects in high fat fed mice.

Material and methods: Mice were surgically implanted with mini-osmotic pumps infusing low dose LPS or saline for 28 days. Mice had free access to water and either a control diet or a RSV supplemented diet.

Results: LPS-treated mice had an increased food consumption, which was not seen in RSV/LPS animals. However, there were no differences in net weight gain after 28 days of treatment. OGTT showed no overall difference in glucose metabolism as area under the curve was the same in all groups. However, LPS-treated mice had a small but significant reduced hyperglycemia 15 min after glucose dose. Importantly, fasting insulin was elevated in LPS-treated mice. RSV was able to prevent this hyperinsulinemia. Gene expression of peptide hormones of the distal small intestine was not affected by LPS or RSV.

Conclusion: Resveratrol has promising effects on insulin resistance induced by chronic low-grade inflammation in rodents. Further studies are needed in order to pinpoint the precise molecular pathways involved in this effect.

P14.02 Mads Vandsted THE ROLE OF ATGL AND G0/G1 SWITCH GENE COMPLEX IN LPS INDUCED Svart KETOACIDOSIS

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Background: Type I diabetes is characterised by absolute lack of insulin production. In case of insufficient levels of insulin the release of free fatty acids (FFA) is stimulated. This leads to the formation of ketone bodies. The steps in the process of FFA release is not very well described in literature, although it is assumed that well known lipases like hormone sensitive lipase and adipose tissue triglyceride lipase (ATGL) participate.

Aim: To define whether stimulation of ATGL and suppression of G0/G1 switch gene occur in the initial phases of diabetic ketoacidosis and thus can be identified as the primary mechanisms behind this life threatening condition. To accomplish this we intend to develop a new human model that is as close to reality as possible, by utilising LPS to mimic an infection.

Methods: The study will be a single blinded, controlled, randomized, crossover study including 2 study days separated by at least 3 weeks. 9 male subjects with type 1 diabetes are enrolled.

Intervention day: The subjects are given one dose of LPS early in the morning and regular insulin is reduced to 10%. Muscle and adipose tissue biopsies are performed to assess lipase activity (ATGL, G0/G1 switch gene), GH and insulin signalling via phosphorylation and expression of proteins involved in signalling and regulation of lipid metabolic enzymes.

Results and perspectives: This study will contribute with new knowledge

about pathogenic mechanisms leading to ketosis and frank diabetic ketoacidosis in patients with type 1 diabetes. We use a new LPS model which is more realistic than insulin withdrawal and investigate the specific role of the rate limiting ATGL, G0/G1 switch gene complex.

- P14.03      Jesper Løkke      EFFECT OF PROTEIN HIGH IN LEUCINE ON MUSCLE PROTEIN BALANCE IN  
Mehlsen      FRAIL ELDERLY PATIENTS. ACUTE STUDY WITH PROTEIN-TRACER-  
TECHNIQUES

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Background: Improved muscle function/strength will enhance the quality of life of the more frail elderly population. Dietary proteins and amino acids act as anabolic substrates in muscles in elderly people. In particular leucine is suggested to have an impact on muscle protein synthesis. Leucine is abundant in whey protein compared to soy protein. However, there is a lack of studies comparing effects of different types of dietary proteins on protein metabolism.

Aim: To examine the acute effects of supplementation with whey compared to soy protein and control without protein on muscle protein synthesis, protein balance and insulin sensitivity in elderly fragile women.

Methods: We include 10 frail women, age 60-85 years in a randomized crossover study. To define fragility we will use the Women's Health and Ageing Studies (WHAS) criteria of fragility: 1) Low body weight 2) Everyday exhaustion 3) Low energy expenditure 4) Slow walking 5) Grip strength weakness. The subjects are their own controls in 3 intervention blocks of 4 days duration A: whey protein 45 gr./day, B: soy protein 45 gr./day or C: control: maltodextrine(iso-caloric). Intervention blocks are conducted with a 4 week washout period between them. On the 4th day postprandial protein synthesis will be measured over 4h using a tracer infusing protocol with  $^{15}\text{N}$ phenylalanine along with a two-hour hyperinsulinemic euglycaemic clamp, blood samples and muscle biopsies. In muscle biopsies mTor and sites downstream from mTor is quantified using western blotting for analysing steps of signaling in muscle protein synthesis initiated by leucine. Whole body protein kinetics are calculated using the formular  $Q=i \cdot E_i/E_p-i$ .

- P14.04      Thomas      METABOLIC SIGNALING IN HUMAN MUSCLE AND ADIPOSE TISSUE  
Schmidt Voss      FOLLOWING HYPOGLYCEMIA.

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Hypothesis: Hypoglycemia counteracts insulin signaling via hormone-dependent intracellular counter-regulatory mechanisms, involving phosphorylation of specific signaling proteins.

Aim: To define counter-regulatory mechanisms in muscle- and fat tissue during hypoglycemia, and to investigate the effect of insulin on lipid metabolism in healthy subjects.

Design: Randomized, controlled, single blinded, crossover study.

Materials and methods: 9 healthy men completed three study days: 1) Control (bolus 2 ml saline at t= 0) 2) Hyperinsulineamic hypoglycemia (Bolus insulin 0,1IE/kg i.v. at t=0) 3) Hyperinsulinaemic euglycemia (bolus insulin 0,1 IE/kg i.v. at t=0 and continous 20% glucose infusion i.v. from t=0 to t=105). Biopsies: Muscle tissue was obtained by a Bergström biopsy needle from m. vastus lateralis and subcutaneous fat tissue from the abdomen by liposuction at t= -40 min. t= 30 min. and t= 75min. Phosphorylation of different proteins involved in lipid- glucose and protein metabolism will be analyzed. Blood samples: Blood glucose levels every 5 min. Insulin, c-peptide, adrenaline, glucagon, GH, FFA, cortisol and ghrelin every 15 min. Fat metabolism was estimated using a palmitic acid tracer from t=30 to t=105.

Results: Plasma samples, serum samples and biopsy materials are currently being analyzed.

P14.05 Sascha  
Pilemann-  
Lyberg

URIC ACID ASSOCIATED WITH DECLINE OF GFR IN DIABETIC NEPHROPATHY

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Background and aim: Evidence from epidemiological and prospective studies indicates that serum uric acid (UA) is a risk factor for development and progression of CKD and loss of kidney function. We evaluated the effect of serum UA on change in GFR in patients with type 1 diabetes (T1DM) in a previous conducted clinical trial.

Methods: Post hoc analysis of a clinical intervention trial of the long-term renoprotective effect of losartan 100 mg on progression of diabetic nephropathy in T1DM homozygous for the I (n=26 ) or D (n=27) allele of the ACE/ID polymorphisms. Mean follow-up time was 3 years (range 1.5 - 3.5). Serum UA was measured at baseline. Primary end-point was GFR measured every 6 month. Effect of UA was tested in a linear regression

model with and without adjustment for known progression factors (Gender, HbA1c, systolic blood pressure, cholesterol, baseline GFR and baseline urinary albumin excretion rate (UAER)).

Results: Mean baseline UA was 5.7 mg/dL (SD  $\pm$ 1.8), GFR 87 mL/ min/ 1.73m<sup>2</sup> (SD  $\pm$ 23), Geometric mean of UAER 1023 mg/ 24h (IQR, 631 - 1995). Similar association between UA and change in GFR was present for the two ACE/ID polymorphisms. In an unadjusted linear model UA was positively associated with decline in GFR ( $r^2$  = 0.06, p = 0.09). After adjustment for known progression factors the association increased to a significant level ( $r^2$  = 0.35, p = 0.011). In the backward elimination UA remained in the model, together with baseline UAER and baseline GFR ( $r^2$  = 0.26, p = 0.0031).

Conclusion: Uric acid was positively associated with decline in GFR in type 1 diabetic patients with nephropathy. UA was a significant predictor together with UAER and baseline GFR.

P14.06 Agnethe Berglund

#### THE EPIDEMIOLOGY OF GROWTH HORMONE DEFICIENCY; A NATIONWIDE COHORT STUDY

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Background: Growth hormone deficiency (GHD) is an endocrine disorder associated with increased morbidity and mortality. It may present alone or in combination with insufficiency of other pituitary axes. GHD patients may be substituted with growth hormone (GH). The consequences of GH substitution on morbidity and mortality are unsettled.

Aim: To study relevant parameters for the increased morbidity and mortality in patients with GHD. To evaluate the safety of GH substitution in childhood and adulthood onset GHD, as well as eventual differences of the impact of GHD on morbidity and mortality in patients insufficient on one or more pituitary axes. Medication of co-morbidities and the correlation to morbidity and mortality will be evaluated. Further, changes in outcome between the study cohort and a previous identified GHD cohort will be studied.

Patients and methods: All patients in Denmark diagnosed with hypopituitarism during 2000-2012 will be identified using the National Patient Registry to establish a primary cohort, whereof patient files for all patients will be studied in order to make a definite diagnosis of hypopituitarism. Patients will be matched with 100 controls from the background population. Information from the national registries regarding hospitalizations, deaths and prescribed medication will be retrieved for both patients and controls. Information on substitution of the hypopituitary axes will be retrieved from the hospital pharmacies.

P14.07 Joan Bach  
Nielsen

## J.B. Nielsen

**Conclusion:** Taking into account that some RYGB individuals experienced asymptomatic hypoglycemia, CGM under real-life circumstances can be used to diagnose postgastric bypass hypoglycemia and it may be a useful tool in evaluating the treatment effect, as illustrated for low-carbohydrate dietary intervention.

# THE MACROPHAGE MARKER SOLUBLE CD163 AND ITS ASSOCIATION WITH NEPHROPATHY AMONG INDIVIDUALS WITH SCREEN DETECTED TYPE 2 DIABETES

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**Aim:** Low grade inflammation in adipose tissue characterized by a high amount of activated macrophages is believed to play a central role in the development of insulin resistance and type 2 diabetes. The macrophage derived biomarker soluble CD163 (sCD163) is increased in obese individuals and associated with development of type 2 diabetes in the general population. In the Anglo-Danish-Dutch study of Intensive treatment in People with Screen-detected Diabetes in Primary Care (ADDITION-study), individuals aged 40-69 years with hitherto undiagnosed type 2 diabetes, are identified. We aimed to investigate the association between sCD163 and markers of nephropathy in the Danish arm of the ADDITION-study (ADDITION-DK).

**Material and methods:** In this prospective cohort study, 1446 individuals diagnosed with type 2 diabetes at baseline in 2001-2006 were included. Baseline serum was analysed for sCD163 by ELISA. Markers of nephropathy were assessed by the urinary albumin/creatinine ratio (UACR) and estimated GFR (eGFR). Markers of nephropathy were associated to increased concentration intervals of serum sCD163: <2.0 mg/l, 2.0-3.0 mg/l and >3.0 mg/l.

**Results:** Unadjusted data shows a significant increased UACR at follow up with increased baseline serum sCD163. No significant trend was found on eGFR. Furthermore an increased serum sCD163 was significant associated with increased BMI, systolic blood pressure, HbA<sub>1c</sub>, fasting capillary blood glucose, HDL cholesterol and triglyceride.

**Conclusion:** Increased serum concentration of sCD163 seems to be correlated with increased UACR but not with eGFR among individuals with newly diagnosed type 2 diabetes.

P15.01 Anil Anil

#### RISK OF INFECTIONS AMONG TYPE 2 DIABETES PATIENTS: AN 18-YEAR NATIONWIDE COHORT STUDY

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**Objectives:** The association of Type 2 diabetes (T2D) with increased risk of infections is not supported by strong evidence. We aimed to quantify the incidence of infection hospitalizations among individuals with and without T2D.

**Methods:** We conducted a population-based cohort study of all incident T2D patients (n = 273,633) who were diagnosed between January 1995, and December 2012 in Denmark. We established a comparison cohort by selecting five age- gender- and municipality-matched non-diabetes people from the general population (n = 1,364,762). Infection episodes were identified from discharge diagnoses in the Danish National Patient

Registry. We used Poisson regression to compute incidence rates (IR) per 1000 person-years, and used Cox model to compute rate ratios (RR) adjusted for age, gender, baseline co-morbidities, marital status, alcoholism, and use of statins or steroids.

Results: Among T2D patients, we observed 72,673 (27%) first episodes of infections during a follow-up of 1,236,946 person-years yielding an IR of 58.75 (95% confidence interval (CI): 58.33 - 59.18) per 1000 person-years. In the comparison cohort, 234,144 (17%) episodes of infection were observed during a follow-up of 6,115,964 person-years corresponding to an IR of 38.28 (95% CI: 38.13 - 38.44) per 1000 person-years. In Cox models, the risk of any infection hospitalization was raised with T2D (adjusted RR: 1.60, 95% CI: 1.59 - 1.62), most pronounced for meningococcal infections (adjusted RR: 2.09, 95% CI: 1.27 - 3.41) and septicemia (adjusted RR: 1.97, 95% CI: 1.90 - 2.04).

Conclusions: T2D patients were at much higher risk of infections compared to matched population comparisons.

P15.02      Anne Grethe Schioldan      EFFECTS OF A DIET RICH IN ARABINOXYLAN AND RESISTANT STARCH VERSUS A LOW-FIBRE DIET ON LIPID AND CARBOHYDRATE METABOLISM IN SUBJECTS WITH METABOLIC SYNDROME

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Introduction: Arabinoxylan and resistant starch are important dietary fibre compounds that stimulate colonic short chain fatty acid (SCFA) production. SCFAs are considered to be mediators of positive metabolic effects of dietary fibers.

Objective: To compare postprandial responses of lipid, glucose, insulin, GLP-1 and GLP-2 after a diet rich in arabinoxylan and resistant starch (Healthy Carbohydrate diet, HCD) versus a Western Style diet (WSD) in subjects with metabolic syndrome (MeS). Fecal SCFA was used as marker for diet-induced metabolic changes in colon.

Methods: Nineteen subjects with MeS completed the 4-week randomised, cross-over study. The HCD had a high content of resistant starch (20.7 g/day) and arabinoxylan (16.0 g/day) while only 2.8 g/day resistant starch and 3.6 g/day arabinoxylan were present in the WSD. At start and end of each intervention we measured 1) fecal SCFA, 2) triglycerides, 3) ApoB-48, 4) free fatty acids, 5) glucose, 6) insulin, 7) GLP-1 and GLP-2 responses to a high-fat meal. Responses were calculated as AUC and compared by ANOVA for repeated measurements using subject, diet, period, and

baseline values as covariates.

Results: Fecal butyrate and acetate concentrations were significantly higher after consuming the HCD than the WSD ( $p < 0.01$ ). The lipid, glucose and insulin responses were not altered by the diets. GLP-1 and GLP-2 results will be presented.

Conclusions: A 4-week dietary intervention rich in resistant starch and arabinoxylan versus a low-fiber diet differentially changed the fecal SCFA concentration in subjects with MeS. However, this did not affect lipid or glucose metabolism in the present study.

- P15.03      Anne Sofie Korsholm Nielsen      OBSTRUCTIVE SLEEP APNEA AND THE EFFECT OF CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP), WEIGHT LOSS AND THE BIOACTIVE COMPOUND RESVERATROL ON INFLAMMATION

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Background: Obstructive sleep apnea (OSA) is a highly prevalent disease that is associated with increased morbidity and mortality. OSA is widely recognized as an independent risk factor for insulin resistance, cardiovascular disease and development of type 2 diabetes (T2D). Current evidence suggests that low-grade inflammatory processes play a pivotal role in the pathogenesis. Studies have demonstrated elevated levels of pro-inflammatory markers, such as TNF $\alpha$ , IL8 and CRP in patients with OSA, independent of T2D and obesity. It has been suggested that chronic intermittent hypoxia resulting from OSA is an independent factor, however mechanisms are incompletely understood. Standard treatment for OSA is CPAP, and studies have showed improved insulin sensitivity and reduced inflammatory status following CPAP.

Aim: To investigate the metabolic changes in adipose and liver tissue in order to get a better understanding of how OSA negatively affects whole body metabolism. To evaluate the effect of CPAP, resveratrol and weight loss on inflammation in OSA patients.

Design: We plan to recruit subjects scheduled to undergo intra-abdominal bariatric surgery. Examination will include home screening test for OSA, blood samples and subcutaneous adipose tissue biopsies at baseline. According to the apnea-hypopnea index, subjects will be grouped into "no OSA" or "OSA". Prior to surgery, the OSA group will be randomized to receive treatment with resveratrol, placebo tablets or CPAP for 2 months. During surgery, biopsies will be obtained from liver and adipose tissue. Six months after surgery, we will do a follow-up with the same examinations as at baseline.

- P15.04      Pedram      EFFECTS OF NATURAL AND ENRICHED UNFILTERED COFFEE ON LIVER FAT CONTENT AND GLUCOSE AND LIPID METABOLISM IN NON-ALCOHOLIC

Shokouh FATTY LIVER DISEASE - AN IN-VIVO EVALUATION USING HYPERPOLARIZED MRI BIOPROBES

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An expansive body of epidemiologic and preclinical evidence shows that habitual coffee consumption possess protective effects against insulin resistance syndromes including metabolic syndrome (MetS) and its hepatic manifestation, nonalcoholic fatty liver disease (NAFLD). Coffee is not only able to hinder the development of NAFLD, but also to protect hepatocytes from inflammation and oxidative cellular injury. These substantial findings demand mechanistic studies to bridge the gaps in our understanding on which metabolic pathways and what bioactive substances are involved. To explore this, a rat model of MetS induced by a high-fat/high-carb diet will be used in a controlled pilot study which precedes a main larger study. Animals will be fed brewed unfiltered natural or enriched coffee (with phenolic, diterpenoid, or alkaloid compounds) for 12 weeks. Comparison of the main classes of coffee bioactive substances using hyperpolarized magnetic resonance imaging (H-MRI), may clarify their individual metabolic effects. H-MRI is a state-of-the-art technology which enables picturing the metabolic pathways of pre-polarized bioprobes such as <sup>13</sup>C-pyruvate under in-vivo conditions. Liver fat content will be quantified by NMR spectroscopy and the expression of relevant genes will be assessed by PCR array analysis. Liver and pancreas histopathologic examinations with particular focus on inflammation and apoptosis will also be included. Body composition, insulin resistance (by glucose tolerance testing), and plasma lipids will be monitored regularly. In this project, our ultimate goal is to pinpoint efficacious substances in coffee and their target metabolic pathways in MetS and NAFLD.

P15.05 Michael MR DIAGNOSTICS OF DIABETIC PERIPHERAL NEUROPATHY

Væggemose

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Aim: To evaluate the feasibility of magnetic resonance (MR) imaging to demonstrate peripheral nerve lesions (sciatic, peroneal, tibia and sural) in patients with diabetes.

Methods: T2 weighted spectral selection attenuated inversion recovery (SPAIR) MR images (0.3x0.3x3mm<sup>2</sup>; TR/TE: 5000/47ms) were acquired to measure the extent of the focal nerve lesions at 3 Tesla (Magnetom-Skyra,

Siemens AG, Erlangen, Germany). The MR scans consisted of 16 axial slices of the sciatic nerve above patella and the peroneal, tibia and sural nerve at the mid-calf. Presence and severity of neuropathy were determined based on nerve conduction studies (NCS), vibration perception thresholds (VPT) (index finger/big toe), blood samples and conventional clinical neurological examinations (Neuropathy impairment score (NIS) and Neuropathy symptom score (NSS)).

Results: Cross sectional images of the thigh in a diabetic patient with severe neuropathy (NIS = 52, NSS = 7, NCS = abnormal, VPT = reduced to absent) and a patient without presence of neuropathy (NIS = 4, NSS = 0, NCS = normal, VPT = reduced), show a difference in the signal intensity of the nerves. Furthermore, with an in-plane resolution of  $0.3 \times 0.3 \text{ mm}^2$  the fascicular lesions appear as multiple small hyperintensities in the neuropathic patient.

Conclusion: MR may be developed to serve as a diagnostic tool for earlier diagnosis of diabetic neuropathy. This may help to understand the mechanisms behind the development of this disorder thereby potentially reducing the burden of late stages of diabetic neuropathy including foot ulcers and amputations.

P15.06 Elias Sundelin PHARMACOKINETIC IMAGING OF METFORMIN USING [ $^{11}\text{C}$ ]METFORMIN

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Objectives: Metformin is the most widely used oral antidiabetic drug. It has well documented effects on glycemic control, and has been shown to reduce the risk of diabetes associated mortality including cardio-vascular death. Yet, the therapeutic effects of metformin vary considerably from patient to patient and this is likely due to individual variations in the pharmacokinetic properties of the drug. To investigate the biodistribution of metformin in humans, we have labeled the drug with carbon-11 and use PET to characterize the pharmacokinetics properties of [ $^{11}\text{C}$ ]metformin.

Methods: 12 subjects were investigated twice. First after injection with a bolus of 200MBq [ $^{11}\text{C}$ ]metformin (10 µg metformin) intravenously followed by 90 min whole body scanning using Siemens Biograph TruePoint 64 Integreret PET/CT. A second scan was performed after the subjects had ingested 100 MBq [ $^{11}\text{C}$ ]metformin orally. Results: [ $^{11}\text{C}$ ]metformin uptake in the kidneys and lesser in the liver and salivary glands could clearly be detected after intravenous injection of the tracer. [ $^{11}\text{C}$ ]metformin dosed orally revealed a predominant uptake located to the gut during the 90 min scan, but detectable uptake in liver and kidney was also demonstrated. No uptake is seen in striated muscle tissue or adipose tissue. No adverse effect was seen during or after the tests.

Acknowledgements: Our data demonstrate that the pharmacokinetic properties of metformin can be investigated in vivo using [11C]metformin PET in humans. The technique therefore holds great promise as a tool to optimize treatment of type 2 diabetes.

P15.07      Henrik Holm  
Thomsen

#### REFUTING ENDOTOXIN TOLERANCE IN HUMANS

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Introduction: Administration of endotoxin in human trials is widely applied as a model of acute inflammatory disease. It is well-known that tolerance to endotoxin ensues with endotoxin exposure. However, the duration of endotoxin tolerance beyond a few days has not been adequately addressed.

Aim: We aim to confirm the occurrence of endotoxin tolerance in humans and quantify its duration.

Methods: 18 healthy, young men were exposed to endotoxin (e.coli lipopolysaccharide) on two separate occasions with varying time intervals. Inflammatory responses to endotoxin were quantified with measures of heart rate, mean arterial blood pressure and temperature along with various cytokines.

Results: Reported as ratio of area under the curve between trial days, we found TNF- $\alpha$  0.85 (95% CI 0.66-1.06, p=0.16), IL-1 $\beta$  0.93 (95% CI 0.79-1.08, p=0.34), IL-6 0.93 (CI 95% 0.70-1.16, p=0.52), IL-10 1.26 (95% CI 0.88-1.64, p=0.16) and cortisol 0.91 (95% CI 0.81-1.00, p=0.052). Vital signs ratios between trial days were similarly insignificant except for heart rate that was an average of 16.67 % higher on the second trial day (95% CI 1.01-32.21, p=0.04). The median interval was 76 days (interquartile range 48-90).

Conclusion: Our study shows no significant tolerance to re-stimulation with endotoxin when interval is longer than previous studies applied. This is a novel finding. Thus in practice, future human trial designs with repeated endotoxin exposures warrants little consideration of tolerance.

P15.08      Rikke  
Hjortebjerg

#### IGFBP-4 FRAGMENT LEVELS ARE UNAFFECTED IN PATIENTS WITH ST-ELEVATION MYOCARDIAL INFARCTION TREATED WITH HEPARIN AND PCI

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**Background:** Circulating levels of pregnancy-associated plasma protein-A (PAPP-A) predict outcome in patients with acute coronary syndrome (ACS). Unfortunately, administration of heparin to patients with ACS increases circulating PAPP-A. By contrast, PAPP-A-derived N- and C-terminal fragments of insulin-like growth factor binding protein-4 (NT-IGFBP-4/CT-IGFBP-4) may be unaltered and serve as superior biomarkers in ACS.

**Methods:** We prospectively included 78 patients with ST-segment elevation myocardial infarction (STEMI) treated with percutaneous coronary intervention (PCI). Prior to PCI, patients were injected with 10,000 IU of unfractionated heparin (UFH). Blood samples were collected immediately before PCI, but after UFH-injection; immediately after PCI and on day 1 and day 2. Plasma IGFBP-4, CT-IGFBP-4 and NT-IGFBP-4 levels as well as serum PAPP-A and IGF-I were determined by immunoassays.

**Results:** Plasma PAPP-A was strongly elevated upon STEMI, UFH-administration and PCI with mean concentrations (95%-confidence interval) pre-PCI, post-PCI, day 1, and day 2 of 13.0 (11.2;15.2), 14.8 (13.1;16.8), 1.03 (0.90;1.18), and 1.08 (0.92;1.28) µg/l, respectively ( $p < 0.0001$ ). Concentrations of IGFBP-4, CT-IGFBP-4 and NT-IGFBP-4 pre-PCI were 154 (142;166), 53 (47;60) and 136 (122;150) µg/l, and levels were unaltered post-PCI. Concentrations increased on day 1 by 63 (43;87)%, 69 (36;110)%, and 47 (21;79)%, respectively ( $p < 0.0001$ ), i.e. at a time point when PAPP-A levels had normalized.

**Conclusion:** Plasma IGFBP-4-fragments levels are not acutely altered in patients with STEMI treated with heparin and PCI. Alternatively, they possess potential as prognostic markers in ACS patients.

P16.01      Shun-Ichi  
                 Suzuki

BLOOD OXYGENATION OF THE MASSETER MUSCLE DURING SUSTAINED ELEVATED MUSCLE ACTIVITY

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**Background:** Myofascial pain associated with temporomandibular disorders has been linked to hyperactivity and sustained contractions of craniofacial muscles that may lead to pain. Different contraction levels of the masticatory muscles may result in changes on blood flow. Lately, it has been suggested that chronic muscle pain may be related to localized disturbances of intramuscular blood flow leading to a lower level of oxygen distribution, hypoxia and microcirculatory changes that may involve subclinical inflammatory characteristics changes in the affected

tissue facilitating pain.

**Aim:** Assess the hemodynamics in the craniofacial muscles during experimental sustained elevated muscle activity (ESEMA) in healthy subjects.

**Materials and methods:** Preliminary results of 5 subjects are presented in this abstract. Hemodynamic characteristics of the masseter muscle were measured with a laser blood oxygenation monitor during intercalated clenching and resting periods of 1 min for 1 hr. During clenching periods, the volunteers bit on a bite force transducer device at 10% or 40% of their maximal voluntary clenching (MVC). The data was analyzed by ANOVA: factors of Condition (Bite or Rest), Force (10 or 40% MVC) and Time (data grouped and averaged every 10 min).

**Results:** ANOVA showed an overall effect of time on OXY-Hb ( $p=0.006$ ) and Total Hb ( $p<0.040$ ); of condition on de-OXY ( $p=0.045$ ). There were interactions between condition with force on OXY-Hb ( $p=0.017$ ) and Total Hb ( $p<0.004$ ), and condition with time on de-OXY Hb ( $p=0.037$ ).

**Conclusions:** Results shows signs of possible hemodynamic changes occurred during ESEMA.

**Acknowledgment:** This study is supported by Aarhus University.

P16.02      Line Staun      FLUORIDE IN DENTAL BIOFILM AND SALIVA

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**Background:** Many studies have measured concentrations of fluoride (F) in saliva. Considering that biofilm is of vital importance in caries control focus has now turned towards F in biofilm reservoirs, with the potential to increase F in the caries process. Only a few studies have measured F in biofilm and saliva concomitantly or examined F in biofilm at different sites in the oral cavity. For this reason it is important to conduct studies comparing the dynamics of F in biofilm and saliva as well as exploring the site-specificity of F in dental biofilm.

**Method:** We plan to use the inverted F-electrode method (Vogel et al. 1990) for the F measurements. A half-cell conventional F-electrode is cut and positioned upside down. The application of the samples directly onto the electrode plus manipulation and dilution (buffer; TISABIII) are performed under a microscope using a pulled capillary as a pipette. A micro-reference electrode and a potentiometer complete the circuit. A crucial step in handling the samples is to ensure that they are covered with oil all the time to prevent evaporation. Using a modified conventional F-electrode in this way permits analysis of nanoliter samples ( $<1 \mu\text{L}$ ) with great precision and without loss of accuracy. This is of utmost importance since we are dealing with extremely small biofilm samples. Even small changes in the F concentration are potentially significant.

**Perspectives:** The aim of the studies is to implement the inverted F-



electrode method and gain new knowledge on the dynamics of F in biofilm and saliva. Further knowledge on this topic may lead to the development of new and more efficacious methods for caries control.

P16.03      Mats Bue      PHARMACOKINETICS OF VANCOMYCIN IN PORCINE BONE OBTAINED BY MICRODIALYSIS

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Background: Traditionally, the pharmacokinetics of antimicrobials in bone has been investigated using bone biopsies, which suffers from considerable methodological limitations. Microdialysis (MD) offers an attractive alternative to obtain bone concentrations of antimicrobials.

Aim: The aims of this study were to investigate the suitability of the MD method for vancomycin measurement in a laboratory setting and to apply MD for measurement of vancomycin in subcutaneous tissue, cancellous and cortical bone.

Materials and methods: Laboratory studies were conducted to determine in vitro recovery by gain and by loss (1-25 µg/ml), appropriate flow rate, calibration concentrations and the effect of temperature and concentration on recovery. In an experimental study MD catheters were placed in subcutaneous tissue and in cancellous and cortical bone. CMA 63 catheters were in bone placed in drill holes. All dialysates were analysed using an UHPLC method. Vancomycin concentrations in plasma were determined using cobas (c501, Roche). Verification of catheter locations was performed by autopsy, and intra cortical placement of drill holes was verified by post-mortem CT.

Results: Laboratory study: Recovery by gain equalled recovery by loss, and was independent of the concentration. Recovery increased slightly with increasing temperature. Porcine study: For all extravascular tissues, a heterogeneous distribution of vancomycin was demonstrated. AUC were lower for bone, cancellous as well as cortical when compared to free plasma.

Conclusions: MD is a reliable method for obtaining concentrations of vancomycin. We found a delayed and decreased penetration of vancomycin from plasma to bone.

P16.04      Simple      SOMATOSENSORY ASSESSMENT AND CONDITIONED PAIN MODULATION  
Futarmal      IN TEMPOROMANDIBULAR DISORDERS PAIN PATIENTS  
Kothari

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The pathophysiology and underlying pain mechanisms of temporomandibular disorders (TMD) are poorly understood. Aims were to assess somatosensory function at temporomandibular joint (TMJ) and examine whether conditioned pain modulation (CPM) differs between TMD pain patients (n=22) and healthy controls (n=22). Quantitative sensory testing (QST) was used to assess somatosensory function. Z-scores were calculated for patients based on reference data. CPM was tested by comparing pressure pain thresholds (PPT) before, during and after the application of painful and non-painful cold stimuli. PPTs were measured at painful TMJ and thenar (control). Data were analyzed with ANOVAs. Relative changes in PPT values during CPM were tested for correlations with absolute PPT values at TMJ and QST findings. 95.5% of the patients had somatosensory abnormalities with somatosensory gain in regard to PPT and mechanical pain stimuli and somatosensory loss in regard to warm and vibration detection as most frequent somatosensory abnormalities. There was a significant CPM effect (increased PPT) at both sites during painful cold application in both healthy controls and patients ( $P<0.001$ ). There was no significant difference in the relative CPM effect during painful cold application between groups ( $P=0.135$ ). There were significant correlations between the relative changes and absolute PPT values during CPM ( $p=0.435$ ,  $P=0.042$ ) and cold detection threshold ( $p=0.465$ ,  $P=0.028$ ). In conclusion, somatosensory abnormalities were commonly detected in TMD pain patients and CPM effects were similar in TMD pain patients and healthy controls and appear to be associated with cold and pressure pain sensitivity.

P16.05      Kristian Friesgaard Christensen      EFFECTIVENESS AND SAFETY OF INTRAVENOUS FENTANYL ADMINISTERED BY AMBULANCE PERSONNEL

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Introduction: In 2011 Central Denmark Region (CDR) decided to authorize all 324 emergency medical technicians, intermediate level (EMT-Is/ambulancebehandlere), to administer intravenous (i.v.) fentanyl.

Methods: Prehospital medical charts from patients treated with i.v. fentanyl in last 6 month of 2012 were retrieved from each ambulance station in CDR. The effectiveness and safety of i.v. fentanyl was evaluated by reduction in pain intensity on the numeric rating scale and by changes in vital signs/use of antidote, respectively.

Results: 1960 medical charts were reviewed. Three major causes of pain were trauma, chest pain and abdominal pain (table 1). Fentanyl provided significant pain reduction (figure 1). However, 60% of the patients had a

NRS > 4 at the end of the transport by ambulance. Pain intensity was different in the three major groups. Fentanyl appeared to be safe with no use of opioid antagonists and a low prevalence of abnormal vital signs concomitant to fentanyl administration.

Discussion: Co-treatment with acetyl salicylic acid and nitroglycerin may explain better pain control for chest pain. Trauma patients and patients with abdominal pain experience different pain modalities (somatic vs. visceral) and, as the effectiveness of opioids may vary with respect to pain mechanism, treatment approaches should be different.

Conclusion: Fentanyl seems to be effective and safe in dosages used in this study. 60% of the patients experience at least moderate pain at the end of transport, presumably a consequence of fentanyl underdosing. Future studies should focus on effect of higher fentanyl dosages and adjustment of treatment with respect to pain mechanism.

P16.06 Bahram  
Ranjesh

IS SELF-REPAIR IN GAPS POSSIBLE? STUDY OF APATITE PRECIPITATION IN THE GAPS BETWEEN THE NEW DENTAL MATERIAL (IMTA) AND DENTIN

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Introduction: Gap at the restoration-tooth interface is always evident, which can cause secondary caries and consequently need for replacement of tooth restorations. Although the optimal use of restorative materials can minimize gap formation, routinely used restorative materials are unable to eliminate the microspaces completely. Novel calcium hydroxide and fluoride releasing dental cement called iMTA has been developed at AU. In a previous study, we found the formation of superficial apatite layer over iMTA in PBS.

Objectives: To evaluate the self-repair ability of iMTA in gaps with different width

Materials and methods: iMTA, Vitrebond, and Fuji IX were tested in the study. Gaps with  $310 \pm 10$  and  $50 \pm 5 \mu\text{m}$  width and 1mm length were made between the restorative material and dentin ( $n = 6$ ). Samples were kept in PBS. Changes in the entrance area of larger gap size were measured with 2D-nucleator by NEW-CAST software. Micro-computed tomography and SEM/EDX were used to confirm gap closure and repair, particularly in smaller gaps.

Results: Use of iMTA resulted in gap closure after immersion in PBS, and complete entrance closure was observed after 96-hours in all iMTA samples. No repair for Vitrebond and Fuji IX was observed.  $\mu\text{CT}$  scans proved the complete gap entrance repair in both gap sizes by iMTA. SEM/EDX showed the repaired area at the entire gap space was calcium

phosphate deposition.

Conclusion: Interestingly, gaps between iMTA and dentin can be filled with calcium phosphate (apatite) deposition in PBS. Accordingly, iMTA possess self-repair ability, which may have a positive effect on prevention of gaps, microleakage, and consequently, secondary caries in dentistry.

P16.07 Kristian Andersen

EFFECT OF UNILATERAL MANDIBULAR DISTRACTION OSTEOGENESIS ON MANDIBULAR MORPHOLOGY IN RABBITS WITH ANTIGEN-INDUCED TMJ ARTHRITIS.

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Background: The aim was to evaluate the effect of unilateral mandibular distraction osteogenesis (MDO) on mandibular morphology in rabbits with antigen-induced arthritis in the TMJ. Materials and Methods: Forty, eight-week-old rabbits were divided into four groups. In Group A and C, arthritis was induced in the right temporomandibular joint. In Group A and B, vertical MDO was undertaken on the mandibular ramus. Group D was control group. On CT scans carried out preoperatively (T0), after distraction (T1), and at euthanasia (T2), cephalometric analysis of mandibular angle (MA), mandibular ramus height (MRH), mandibular collum height (MCH), total posterior mandibular height (TPMH) was performed. Two-factor ANOVA evaluated the effect of MDO and antigen-induced arthritis on the outcome variables. Results: No effect of MDO or arthritis was observed between the groups on MA or MCH. In T0-T1, a positive effect of MDO on MRH and TPMH was obtained in Group A and Group B. In T0-T1, arthritis was not associated with a significant change of mandibular morphology among the treated and untreated rabbits. In T1-T2, a significant negative effect of MDO on MRH in healthy treated rabbits was observed, while no significant differences were observed in rabbits with arthritis following MDO. Arthritis was not associated with a significant effect among the treated rabbits in the observation period. Conclusion: MDO could significantly alter MRH and TPMH in rabbits with antigen-induced arthritis. MDO in rabbits with antigen-induced TMJ arthritis was not associated changes of postoperative mandibular morphology.

P16.08 Natasja Leth Jørgensen

HUMAN CHONDROCYTES CULTURED ON MODIFIED POLYSTYRENE CONSERVE THEIR CHONDROGENIC PHENOTYPE IN VITRO

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Aim: Chondrocytes-based cartilage repair require efficiently expanded chondrocytes, however chondrocytes tend to dedifferentiate under

prolonged expansion culture ex vivo. In this study, we investigated the influence of precipitant induced porosity augmentation (PIPA) modified polystyrene surface on human chondrocytes in vitro.

Methods: Polystyrene was immersed with p-dioxane and prior to cell seeding surfaces were treated with ozone. Human chondrocytes were enzymatically isolated from human cartilage biopsies collected from the inter-condylar groove in distal femur and grown in DMEM/F12 supplemented with 10% FBS, 5 ng/mL bFGF, 1 ng/mL TGFβ3, and 1:100 penicillin-streptomycin (P/S). Chondrocytes in passage 1 (P1) were seeded on; a control surface (a traditional flat polystyrene surface) or PIPA modified polystyrene surface with 10.000 cells/cm<sup>2</sup> in DMEM/F12 supplemented with 10% FBS and P/S. Chondrocytes were cultured until passage 3 and samples were collected for population doubling, RT-qPCR, and pellet culture. Interactions between the independent variables were investigated using Student's ttest and two-way ANOVA (surface#passage). The level of significance was  $p < 0.05$ .

Results: The PIPA surface promoted chondrogenic differentiation of human chondrocytes compared with the control surface culture evident by higher relative gene expression of collagen II and aggrecan. Human chondrocytes expanded on PIPA modified surfaces prior to pellet formation revealed a better chondrogenicity by more synthesis of proteoglycans and collagen II.

Conclusions: Cultivation of human chondrocytes on the PIPA modified polystyrene surface seems to conserve their chondrogenic expression.

P17.01 Pia Kjær  
Kristensen

HIGHER HIP FRACTURE UNIT VOLUME ASSOCIATED WITH POORER QUALITY OF INHOSPITAL CARE, LONGER LENGTH OF STAY AND INCREASED 30-DAY MORTALITY

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Background: Higher patient volume of health services has been linked with better outcomes for a range of surgical procedures, however, little is known about the impact of patient volume on quality of care and outcome among patients with hip fracture.

Objectives: We examined the association between patient volume in hip fracture units and 30-day mortality, quality of care, surgical delay and length of stay.

Methods: Using prospectively collected data from the Danish Multidisciplinary Hip Fracture Registry, we identified 12,065 patients ≥65 years who were admitted with a hip fracture between March 2010 and November 2011. Patient volume was divided into three groups; ≤ 170, 171 to 350 and ≥ 351 admissions per year based on the distribution of the units. Data was analyzed using regression techniques while controlling for

P17.02	Thomas Dahl Nielsen	DURATION OF ANALGESIA AFTER FEMORAL NERVE BLOCK WITH BUPIVACAINE AND DEXAMETHASONE IN PATIENTS WITH FEMORAL NECK FRACTURE
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**Aim:** The aim of our study is to investigate if more patients with hip fracture experience lasting preoperative analgesia from the time of the nerve block until the time of operation or an analgesic duration of at least 24 hours, after a femoral nerve block is done with the addition of Dexamethasone.

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P17.03 Bjørn Borsøe Christensen LIMITED OSTEOCHONDRAL REPAIR BY A BIOMIMETIC COLLAGEN SCAFFOLD - ONE TO THREE YEARS CLINICAL AND RADIOLOGICAL FOLLOW-UP

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Introduction: Treatment of osteochondral injuries is challenging and no gold standard has been established. Cell--free scaffolds are a new treatment option.

Aim: The aim of this study was to evaluate the osteochondral repair in patients treated with the MaioRegen scaffold, a cell--free biomimetic scaffold consisting of Coll 1 and hydroxyapatite. The scaffold has previously shown promising clinical results.

Methods: Ten patients with osteochondral lesions in the knee or in the talus (6:4) were enrolled. The patients underwent preoperative MRI, and CT scans at 1 and 2.5 years postoperative. The cartilage and bone formation was evaluated using the MOCART score and semi-quantitatively, respectively. Knee patients were clinically evaluated using KOOS, IKDC and Tegner scores, while ankle patients were evaluated using AOFAS Hindfoot and Tegner scores.

Results: Two patients were re-operated and excluded from the study due to treatment failure. None of the patients had complete regeneration of the subchondral bone evaluated using CT. At 2.5 years 6/8 patients <10% bone formation in the defects and 2/8 had 50-75% bone formation in the defects. MRI showed no improvement in the MOCART score at any time point. The IKDC and the KOOS pain subscale significantly improved at 2.5 years. No improvement was found with the remaining KOOS subscales, the Tegner or AOFAS score.

Conclusion: Treatment of osteochondral defects with the MaioRegen scaffold resulted in incomplete cartilage and subchondral bone repair at 1 and 2,5 year's follow--up. Some subjective clinical improvement was observed. These results raise concerns about the biological potential of the MaioRegen implant for osteochondral repair.

P17.04 Daan Koppens PROMISING RESULTS OF THE SIGMA UNICOMPARTMENTAL KNEE ARTHROPLASTY, 1-YEAR FOLLOW-UP WITH RSA

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Introduction: The Sigma UKA is relatively new on the market. Data of the Australian arthroplasty register show a cumulative percent revision rate for the Sigma UKA of 1.6 (0.5-5.0) and 2.3 (0.8-5.9) for the first and second years indicating a low revision rate. Early implant migration measured by radiostereometric analysis (RSA) is a predictor of late implant loosening/revision. We evaluate migration of the Sigma UKA with currently 1-year follow-up.

Methods: 47 knees in 46 patients (21 Male) with a mean age of 63Y (SD 9.7) were operated with a fixed-bearing medial Sigma UKA. Stereoradiographs were conducted post-operative, at 4 months (4M) and 1 year (1Y) after surgery. Model-based RSA was used for migration analysis of both the femoral and tibial component.

Results: There was no continuous migration between 4M and 1Y follow-up for any translation or rotation. Median difference MTPM between 4M and 1Y for both the femoral (1.07) and tibial (1.07) component was similar ( $p=0.58$  and  $p=0.15$ , respectively). None of the patients had been revised. The presented 1-year data is based on 30 patients.

Conclusion: Preliminary results of 1-year RSA follow-up of Sigma UKA show promising results. No migration between follow-ups was observed for either the femoral or the tibial component. The cohort will be followed until minimum 2 years after surgery to determine if there is ongoing migration.

- P17.05      Rehne  
Lessmann  
Hansen
- EVALUATION OF PERI-IMPLANT BONE MINERAL DENSITY CHANGES AFTER FEMORAL OSSEOINTEGRATED PROSTHESIS SURGERY
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- Background: Trans-femoral amputees have reduced bone mineral density (BMD) in the residual femur, hip and ipsilateral pelvis. Insertion of an osseointegrated (OI) prosthesis may affect the BMD additionally.
- Purpose and aim: To study the effects of unloading/loading and stress shielding after OI-prosthesis surgery.
- Materials and methods: 20 patients (13 males) of mean age 48 (range 30-66) years were operated with an OI femoral implant in two stages. DXA scans were performed at baseline (postoperative) and in intervals according to changes in rehabilitation (3, 6, 9, 12, 18 months). The first 9 months non- weight bearing (nWB) was allowed, and after 9 months weight bearing (WB) was encouraged. The femoral peri-implant bone was evaluated in 3 regions of interest (ROIs), proximal (Rp), and medial (Rm) and lateral (Rl) to OI implant.
- Results: From baseline to 18 months follow-up total peri-prosthetic BMD was unchanged ( $p=0.11$ ). However, during nWB periprosthetic BMD decreased by 26% CI(6.9;48)  $p=0.01$  and during WB BMD increased by 31% CI(2;51.5)  $p=0.04$ . All 3 periprosthetic ROIs had a decrease in BMD during the nWB rehabilitation period with a significant decrease in Rp of



44% CI(23;68)  $p=0.0002$ . During WB rehabilitation, BMD increased in all three ROIs with a significant increase in RI by 34% CI(5;54)  $p = 0.03$ .

Conclusion: Unloading of the residual femur in the first 9 months after IO implantation causes pronounced stress-shielding and peri-implant BMD loss. Increased or full loading of the residual femur between 9 and 18 months increases BMD, but not to baseline values. Patients will be followed to investigate additional effect of direct femoral bone loading from the IO implant.

P17.06      Morten Lykke      CARTIGEN PRO® FOR CARTILAGE REPAIR  
                 Olesen

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Aim: to investigate the hyaline cartilage regenerative ability of the Cartigen Pro® scaffold (CartPro) in a chondral defect in a porcine model. The scaffold treatment was compared with the gold standard treatment, microfracture (MFx).

Materials and methods: CartPro scaffolds were produced using rapid prototyping for plotting of a polycaprolactone (PCL) backbone structure. Lyophilising a water-PCL-dioxane solution created micro- and nano-pores. Ten skeletally mature Göttingen minipigs received a cylindrical full thickness chondral defect ( $\varnothing=6\text{mm}$ ) in the medial aspect of the femoral trochlea in both knee joints ( $n=20$ ). The defects were randomized into two groups: 1) MFx treatment, and 2) MFx + CartPro ( $\varnothing=6\text{mm}$ ,  $h=0.8\text{ mm}$ ). MRI scans were performed at baseline, three and six months. Observation period was 6 months. Gross appearance and radiological evaluation was made using ICRS Macroscopic score and MOCART score, respectively. O'Driscoll score will be used for histological evaluation.

Results: The macroscopic assessment showed lower score for the MFx + CartPro when compared with MFx ( $p=0.03$ ). No significant difference was found in the MOCART score. Histological evaluation is pending (November 2014)

Conclusion: Complete regeneration of the cartilage was not seen in any of the treated knees. The data demonstrated a biological effect of the Cartigen Pro® scaffold, which is primarily related to the subchondral bone region in the defect area. The macroscopic appearance of the defects treated with Cartigen Pro® scaffolds demonstrated a limited integration of the scaffold with the surrounding cartilage. More conclusive outcome will be provided by the histological analysis.

P17.07      Lone Dragnes      UNSCHEDULED CONTACTS WITH HEALTH SERVICES AFTER OUTPATIENT  
                 Brix                      KNEE ARTHROSCOPY: PRELIMINARY RESULTS FROM AN OBSERVATIONAL  
   FOLLOW-UP STUDY

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Background: Good pain management after outpatient surgery is essential to achieve a short recovery time, early discharge and rapid return to daily living. However, studies have shown that pain remains one of the most common problems after outpatient surgery. Postoperative pain may lead to unscheduled contacts with health services.

Aim: To assess the frequency, causes, and results of unscheduled contacts with health services within the first week after outpatient surgery with special emphasis on pain. To document target areas for quality improvement interventions in outpatient postoperative pain treatment.

Materials and methods: In this observational follow-up study, outpatients scheduled for elective knee arthroscopy were enrolled at the Day Surgery Unit at Horsens Regional Hospital. One week after surgery, patients received an electronic questionnaire concerning the post-discharge period.

Results: A total of 155 consecutive patients were enrolled. After discharge, 23 % of patients contacted healthcare service and 15 % had more than one unscheduled contact. Pain was the leading cause. Most contacts were made by telephone the day after surgery either to the Day Surgery Unit or the general practitioner. Even though 95 % of patients reported having received sufficient information and guidance regarding pain and pain-treatment after discharge, the most frequent result of contact was information and guidance.

Conclusion: Although patients received oral and written information, 23 % still contacted healthcare services after discharge during the first week after surgery. Expected future findings: Unscheduled contacts after outpatient surgery differ according to surgical procedures.

P17.08     Ahmed Abdul- A NOVEL TREATMENT TECHNIQUE WITH STEM CELLS (MSC) AND MINCED  
Hussein Abood CARTILAGE FOR THE PREVENTION OF PHYSEAL BONE BRIDGE  
FORMATION IN A STANDARDIZED EXPERIMENTAL PORCINE MODEL

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Background: The cartilaginous growth plate (physis) is responsible for longitudinal bone growth. Due to the vulnerable nature of the physis, it is highly susceptible to injuries. Fractures involving the physis can lead to the formation of a physeal bone bridge, which can cause angular bone deformities and arthrosis.

Aim: The aim of the present project is to combine autologous bone marrow-derived MSC and minced autologous cartilage for prevention and treatment of physeal bone bridges after injuries.

Materials and methods: Six immature pigs (12 weeks) ( $\sigma = 0.4$ ;  $\mu = 0.5$ ;  $\alpha = 0.05$ ; power = 0.80) are used. One week prior to treatment a bone marrow sample will be collected from the iliac crest and centrifuged using a Ficoll® gradient, and cultured in vitro. Plastic-adherent cells will be categorized as MSCs. To induce bone bridge formation the proximal lateral physis in the tibia and the distal lateral physis in the femur will be injured in both hind legs. The physis will be injured by drilling laterally, using a 6 mm cannulated drill under fluoroscopic guidance. In the femur, a gel-filled defect will be compared to an empty defect. In the tibial physis, MSCs loaded into a gel will be deposited in the defect, whilst minced autogenous cartilage, harvested from non-weight bearing part of the knee joint, will be added to the gel, along with MSCs for deposition in the contra-lateral tibia. The pigs will be observed for 12 weeks postoperatively and following euthanization with an overdose of pentobarbital (40mg/kg) specimens will be obtained for further analyses.

P17.09      Eva Natalia  
                 Glassou

LONG TERM ASSOCIATION BETWEEN HOSPITAL PROCEDURE VOLUME AND REVISION AFTER TOTAL HIP ARTHROPLASTY: A STUDY WITHIN THE NORDIC ARTHROPLASTY REGISTER ASSOCIATION DATABASE

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Background: Total hip arthroplasty (THA) is a common procedure which improves pain and function in patients with osteoarthritis. Concurrently, with increased awareness of health-care utilization and costs, the effect of health care provider related elements including hospital procedure volume are of relevance.

Aim: To examine if hospital procedure volume was associated with the risk of revision after THA in the Nordic countries from 1995 to 2011.

Methods: The Nordic Arthroplasty Register Association (NARA) was used to get information about primary THA, revisions and annual hospital volume in Finland, Norway, Sweden and Denmark. Hospitals were divided into 5 volume groups (1-50, 51-100, 101-200, 201-300, >300). Primary outcome was the cumulative incidence of first time revision due to any cause 1, 2, 5, 10 and 15 years after primary procedure. Multivariable regression with death as a competing risk was used to assess the relative risk of revision

(RR).

Results: 416, 212 primary THA were included. The cumulative revision incidence increased from 1.1 (CI 1.1 - 1.2) after 1 year to 9.4 (CI 9.1 - 9.6) after 15 years. At 1 and 2 years no differences in RR were seen between the volume groups. At 5 years RR were reduced for group 51-100 (0.9, CI 0.7 - 1.0), group 101-200 (0.8, CI 0.7 - 0.9) and group 201-300 (0.8, CI 0.7 - 0.9) compared to group 1-50. Same pattern were seen after 10 years while only group >300 showed a reduced RR after 15 years (0.8, CI 0.6 - 0.9).

Conclusion: This study showed a consistent association between hospital procedure volume and long term risk of revision, acknowledging the general centralization that has taken place in the treatment of THA.

P17.10      Steffan Tábori      HIGHER UHMWPE WEAR RATE IN CEMENTLESS COMPARED WITH  
Jensen                              CEMENTED CUPS WITH THE SATURNE® DUAL-MOBILITY SYSTEM

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Background: Displaced medial femoral neck fracture (FNF) may be treated with primary arthroplasty. Dual-mobility articulations have advantages on stability and range of motion. However, polyethylene (PE) wear on two articulating sides might lead to excessive wear.

Purpose: To investigate PE wear rate of primary DM cups in patients with acute FNF.

Materials and methods: From 2005-2011, 414 consecutive patients were operated with Saturne DM cups, 28mm femoral metal heads, UHMWPE. Cementless cups were coated with hydroxyapatite (HA). 239 cups were cemented and 175 were press-fit by choice of the surgeon. In 2012, at minimum 1-year follow-up, 155 patients were dead and the remaining 259 were invited for clinical follow-up. 133 patients were evaluated with 2D wear and wear rate (PolyWare software 3D Pro).

Results: At a mean follow-up of 2.8 (1.0 - 7.7) years, the mean wear was 0.80 (sd 0.4, 0.3-2.5) mm and wear rate was 0.36 (sd 0.28, 0.05-1.70). Wear rate of 0.91 (sd 0.05) in cementless cups were higher ( $p=0.0003$ ) than 0.67 (sd 0.04) in cemented cups. Patients with cementless cups were younger (73.2 vs. 77.2 years,  $p=0.02$ ). Mean cup inclination was 44 (26-65) degrees. There was no correlation between cup inclination and wear ( $p=0.61$ ) and no difference in wear between gender ( $p=0.50$ ). There was correlation between age at time of surgery and wear rate ( $p=0.06$ ). Cup inclination was similar ( $p=0.13$ ) for cemented and cementless cups.

Conclusion: At short term follow-up, we found a higher wear rate in cementless HA coated cups compared with cemented cups. In general mean 2D wear and wear rate in these old and low demand patients was high and above the osteolysis threshold (0.1 mm).

- P18.01      Janne Brammer Damsgaard      THE ILLNESS TRAJECTORY OF SPINE FUSION PATIENTS. A FEELING OF BEING (IN)VISIBLE
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- Background: Research shows that being a back patient is associated with great personal cost, and that back patients who undergo so-called spine fusion often experience particularly long and uncoordinated trajectories. The patients describe a feeling of being mistrusted and thrown around in the system.
- Aim: This study aims to examine how spine fusion patients experience their illness trajectory and hospitalisation.
- Methods: The study is based on qualitative interviews, and the data analysis is inspired by the French philosopher Paul Ricoeur's phenomenological hermeneutic theory of interpretation. Data were collected through observations and semi-structured interviews at an Elective Surgery Centre in a Danish regional hospital.
- Results: The results show that experiences related to prolonged contact with the healthcare system and healthcare professionals are often dismissed as irrelevant. It is also evident that spine fusion patients are denied the opportunity to verbalise what it feels like to, for example, be "a person in constant pain" or someone who "holds back" to avoid being an inconvenience. These feelings are internalised as a sense of doubt and powerlessness, resulting in spine fusion patients experiencing that they are "disappearing" as a person; losing their identity.
- Conclusion: The biomedical perspective obscures spine fusion patients' horizon of meaning, which is existentially rooted in the areas of the lifeworld. This can lead to psychological and social problems, which in turn can result in a compromised sense of identity and a reduced feeling of social belonging.
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- P18.02      Mette Holland-Fischer      RHEUMATOID ARTHRITIS AND MORTALITY FOLLOWING HOSPITALIZED PNEUMONIA; A POPULATION-BASED COHORT STUDY WITH DIAGNOSIS VALIDATION
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- Background: Rheumatoid Arthritis (RA) is associated with reduced lifespan. Increased frequency of severe infections compared with non-RA individuals may be one of the reasons. Little is known about whether RA is

associated with an increased mortality following pneumonia.

Objective: To examine whether patients with RA being hospitalized with pneumonia have a worse prognosis than patients without RA.

Research design and methods: Population-based cohort study of adults with a first-time hospitalization for pneumonia between 1997 and 2011 in Northern Denmark. Information on RA, comorbidity and pneumonia was obtained from medical databases. The diagnosis of RA was validated using 3 definitions of RA in a sample of 200 patients. Mortality was ascertained from the Danish Civil Registration System. Regression was used to compute the adjusted mortality rate ratio (MMR) within 30 days and 90 days following pneumonia hospitalization among patients with and without RA, controlling for sex, age, level of comorbidity, alcoholism and pre-admission antibiotics.

Results: In total 1249 (1.5%) of 80995 hospitalized pneumonia patients had RA. The 30-day mortality was similar among patients with RA (14.7%) and without RA (14.0%) whereas 90-day mortality was 21.9% and 20.4%, respectively. Corresponding crude 30- and 90-day MRRs were 1.05 (95% CI: 0.91-1.22) and 1.08 (0.96-1.22) and adjusted MRRs were 0.97 (0.83-1.12) and 0.96 (0.85-1.08), respectively.

Conclusions: RA was not associated with increased 30- or 90-day mortality following hospitalization for pneumonia. Future analysis will explore associations between RA disease activity, RA medication, calendar time, and pneumonia outcome.

P18.03 Yongfu Yu

#### MORTALITY TRENDS AND LEVELS IN CHILDREN AGED 0-9 YEARS: A NATIONWIDE COHORT STUDY FROM THREE NORDIC COUNTRIES

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Background: Under-five mortality has already been widely studied, while mortality in later childhood receives little attention. The lack of detailed data has been an obstacle to have a basic understanding of mortality trend over age. The unique data from national registers in three Nordic countries provide great opportunities to more accurately characterize mortality trend in children aged 0 to 9 years old.

Methods: The population-based register study used nationwide data in Denmark, Sweden and Finland. The children entered the cohort after birth and follow-up ended at the following events: death, emigration, the day before the 10th birthday or end of follow-up, whichever occurred first. Cumulative mortality and mortality rate stratified by sex, age groups, type of death and calendar periods were used to estimate mortality trend.

Results: A total of 7,105,962 children contributed with person-time to the study and 38,241 deaths were identified. Neoplasms (N=2473) were the dominant cause, followed by disease of nervous system (N=1816) and

Conclusions: Although the three Nordic countries have low mortality rates in children under 10 and mortality rates have decreased during the recent decades, there is still scope for improvement.

*J. Lisander Larsen*<sup>1</sup>, *E. O. C. Hall*<sup>1</sup>, *S. Jacobsen*<sup>2</sup>, *R. Birkelund*<sup>3</sup>

Background: Lupus is a chronic autoimmune disease, affecting mainly women, potentially lethal and quite unpredictable, exposing them to a potential life-threat, and thereby existential uncertainty. Patient existential experiences are scarcely researched, and studies do not emphasize existential themes at stake during the illness trajectory. This leaves a knowledge gap important for evidence-based nursing support.

Results: Interpretation on the existential meaning is in progress. Preliminary results document that the chaotic time of the diagnosis gradually changes over the years, leaving a mark on their existential life. Experiencing the physical unpredictability of the disease is described as a burden, both individually and on relationships, which never diminish. Although the women become more confident with the fluctuations of lupus, their thoughts of new attacks never leave them. The disease flows beneath life as the lurking of a wolf.

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## TOXICITY IN JUVENILE IDIOPATHIC ARTHRITIS

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Background: Juvenile idiopathic arthritis (JIA) is the most common chronic pediatric rheumatic disease. Without treatment the disease causes significant short- and long-term disability and quality of life impairment. Methotrexate (MTX) is a mainstay in the treatment of JIA. However, MTX-induced gastrointestinal toxicity is a significant problem. Studies have shown that more than half of patients with JIA have problems tolerating MTX because of nausea which may lead to cessation of treatment. It is largely unknown why MTX causes nausea.

Aims: Firstly, we wish to determine if single-nucleotide polymorphisms (SNPs) in genes encoding transporter proteins in the liver and intestine are associated to the level of nausea. Secondly, we want to investigate how psychological factors (anxiety, coping strategies) can explain part of the inter-patient variability in the level of nausea.

Methods: Children diagnosed with JIA and treated with MTX will be enrolled in the study. The level of nausea will be determined by an electronic "nausea-diary" and a "Methotrexate-Intolerance-Severity-Score" questionnaire. Blood samples will be used for measurement of the concentration of MTX-polyglutamates in the erythrocytes and determination of the genotype of SNPs in the transporter proteins: SLCO1B1, SLC19A1, ABCC2, ABCB1. Psychological factors are investigated using: nausea-coping-questionnaire; Beck Anxiety Inventory.

Perspectives: To optimize treatment of JIA by using patient SNP genotypes to determine who can tolerate MTX and who cannot. Additionally, identify patients where psychological intervention may diminish MTX-induced nausea.

P18.06 Daniel  
Ramskov  
Jørgensen

THE DESIGN OF THE RUN CLEVER RANDOMIZED CONTROLLED TRIAL: THE FOCUS OF A RUNNING SCHEDULE AND ITS ASSOCIATION WITH THE RISK OF RUNNING RELATED INJURIES.

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Background: The positive effects of running on health outcomes, such as weight loss and cardio respiratory function, are well known. Unfortunately, running is also associated with a high risk of injury. The most recent systematic review reported an overall incidence of 19.4% - 79.3%. If injured,



the median time to recovery is 71 days, with a proportion of 10.7% receiving conservative treatment and a proportion of 4.7% receiving surgical treatment.

**Aim:** The aim of the trial is to investigate if a focus on running intensity compared to a focus on running volume in a running schedule influence the overall injury risk. The trial will take the training variables; progression, frequency, intensity and volume into account and use an objective method of measuring the intensity of running and the running volume.

**Method and design:** The trial is a double blinded randomized controlled trial with a 24 week follow-up. Recreational runners are included. Participants are randomized into two intervention groups following different training schedules: Schedule A (running intensity) and Schedule B (running volume). All participants and members of the diagnostic team are blinded to group allocation. Training data is collected by a smartphone application and GPS. Participants who sustain a running related injury are diagnosed using standardized diagnostic criterias.

**Perspectives:** The trial will result in a better understanding of the causal relationship between the performed running, the risk of injury and the injury developed. Knowledge which can aid in the development of future preventive measures, aimed at developing running schedules minimizing risk of injury, increasing continuity and improving health.

P18.07 Rasmus  
Cleemann

DOSAGES-RESPONS OF BONE MORPHOGENIC PROTEIN ON A BACKGROUND OF SYSTEMIC BISPHOSPHONATE IN AN UNLOADED CANINE IMPLANT MODEL

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A total hip arthroplasty (THA) is used to alleviate people from pain, primarily due to arthrosis of the hip. THA is considered a safe procedure with good results based on registry data. Complications do occur. Fractures near the prosthesis and infections are clear and evident reasons for a revision procedure. A subtle but important reason is aseptic loosening of the prosthesis due to loss of bonestock around the implant. Prior research has shown that a quick bone ongrowth to the metal of the prosthesis increases the prosthesis lifespan. In short, we are interested in having as much bone around the prosthesis as possible! Bonequality is maintained by a coupled balance between bone resorption by osteoclasts and bone formation by osteoblasts. Stimulation of osteoblasts to produce bone will indirectly increase bone resorption by osteoclasts due to coupling between osteoblast and osteoclast activity. The idea behind the project is to increase production and secure bone around the prosthesis. By stimulating osteoblasts with Bone Morphogenic Protein-2 (BMP-2) and block osteoclasts by delayed bisphosphonate administration, we hyphotesize that bone formation will increase and bone resorption will be diminished,

thus increasing prosthesis fixation. We plan to investigate the effect of concomitant anabolic and anti-catabolic stimulations effect on early implant fixation in a paired canine study with 12 animals, with an observation time of 4 weeks. To evaluate the effect of BMP-2 and bisphosphonate, mechanical tests and histomorphometri of the bone/implant interface will be performed to quantify the implant fixation and the effect on a tissue level.

P19.01 Line Kibsgaard MASTOCYTOSIS AND THE RISK OF ANAPHYLAXIS

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Mastocytosis is a rare, heterogeneous group of diseases characterized by an increased accumulation and hyperplasia of mast cells. Based on organ involvement and aggressiveness, WHO have classified seven subtypes. Cutaneous and indolent systemic mastocytosis compose two benign variants, often handled in dermatologic auspices. Similarly to mastocytosis, anaphylaxis has its origin in mast cells, where mediators trigger potentially life-threatening conditions, affecting respiration and circulation.

The association between mastocytosis and anaphylaxis has only been addressed in a few studies. Results are inconsistent and without considerations on obvious confounders such as allergies. Despite this, most guidelines on mastocytosis recommend prescription of epinephrine, regardless of subtype.

We hypothesise that the risk of anaphylaxis is associated with specific subtypes of mastocytosis. Based on data from the Danish National Health Registers, we have designed a retrospective cohort study. We aim to determine which patients should be prescribed epinephrine for acute anaphylactic treatment on a more solid foundation. Secondary it is our aim to determine the risk of concomitant diseases, such as osteoporosis, hematologic cancers and autism spectrum disorders.

P19.02 Alexander Fjældstad OLFACTORY SCREENING: VALIDATION OF SNIFFIN' STICKS IN DENMARK

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Background: The Sniffin' Sticks 12-Identification test (SIT-12) is the most commonly applied Danish olfaction screening tool, however, it has never

been validated in a Danish population. The screening score depends on familiarity with descriptors, which is strongly influenced by linguistic and cultural factors, why validation is mandatory.

Methodology: The SIT-12 was applied to 100 normosmic, healthy Danish participants. Choice of descriptors was registered, along with nasal endoscopic examination, screening for cognitive impairment, depression, and sinonasal symptoms. Descriptors of the original version of SIT-12 were evaluated in 50 participants and misleading descriptors were identified. Modifications to these descriptors were subsequently validated in a comparable group of 50 participants.

Results: Mean odorant identification score in the evaluation group was 11.0 of a possible 12, and 11.6 in the validation group ( $p < 0.0001$ ). Among all odorant identification errors in the evaluation group, 60% were due to 2 of the 12 odorants, lemon and cinnamon. Two descriptors were unfamiliar to more than half the participants. There was a significant difference in the distribution of wrong identification answers between odorants in the evaluation group ( $P < 0.001$ ), but not in the validation group.

Conclusions: The identified systematically wrong descriptors have been modified and validated in the Danish SIT-12.

P19.03      Sandra  
                  Kruchoy  
                  Thygesen

#### RESPIRATORY DISTRESS SYNDROME IN MODERATELY PRETERM INFANTS AND RISK OF EPILEPSY: A POPULATION-BASED STUDY

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Background: Infant respiratory distress syndrome (IRDS) is a common respiratory disorder among preterm infants. The syndrome is known to cause substantial morbidity and increased mortality in early childhood. However, data on long-term morbidity are sparse.

Objectives: To examine the association between IRDS in moderately preterm infants and epilepsy in young adults.

Methods: We conducted this population-based cohort study using individual-level data linkage among nationwide registries. The Danish Medical Birth Registry allowed us to identify all live infants born between 32 and 36 weeks of gestation during January 1, 1978 to December 31, 2009. Using the Danish National Registry of Patients covering all Danish hospitals, we then identified all infants diagnosed with IRDS from January 1, 1978 to December 31, 2009, and computed cumulative incidence of time to first epilepsy diagnosis. We computed hazard ratios comparing children who had IRDS with children who had not, using Cox's proportional hazards regression. The estimates were stratified on gestational age and infant's birth year and adjusted for sex, twin birth, maternal age, and 5-minute Apgar score.

Results: We identified 96,120 children born during 32-36 weeks of gestation. Among these, 6,516 had an IRDS diagnosis as infants. The

cumulative incidence of epilepsy up to age 15 in IRDS patients was 2.0% (95% confidence interval (CI): 1.9%-2.1%). After adjustment, the hazard ratio was 1.4 (95% CI: 1.2-1.6) [1.3 (95% CI: 1.1-1.5) when 5-minute Apgar score was included in the model].

Conclusion: We found that moderately preterm infants with IRDS were at increased risk of epilepsy during early childhood and adolescence.

P19.04 Troels  
Johansen

#### MAPPING LOCAL OXYGEN AND CO<sub>2</sub> TRANSFER RATES IN THE LUNG

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Presently, only a few experimental methods exist to measure local oxygen transfer in the lungs and none for measuring local CO<sub>2</sub> transfer.

Research into pulmonary gas exchange has primarily focused on the distribution of ventilation/perfusion (V/Q) ratios and several imaging modalities have been developed for producing V/Q lung maps. However, in some conditions the anatomical distribution of O<sub>2</sub> and CO<sub>2</sub> transfer rates in the lung are of clinical relevance.

Here we present a new method to estimate the local transfer rates of O<sub>2</sub> and CO<sub>2</sub> based on the local V/Q distributions, making it possible to calculate the fraction of overall gas exchange attributable to individual voxels, regions, sublobes or lobes, as well as demonstrate how the anatomical distributions of O<sub>2</sub> and CO<sub>2</sub> transfer rates differ with disease.

The method is here exemplified using V/Q data obtained from a healthy control by PET/CT imaging. The validity of the method's blood gas algorithm was verified by comparing with the algorithm used in Multiple Inert Gas Elimination Technique (MIGET) studies.

A sensitivity analysis showed that the local values of the estimated gas transfer maps were relatively insensitive to random noise in the input ventilation and perfusion data, whereas they showed sensitivity to errors in the model input values of global V/Q ratio and arterial-venous oxygen content difference.

The data and gas transfer maps produced by this method offer the potential for an improved understanding of pulmonary gas exchange in health and disease as well as being a valuable teaching tool.

P19.05 Kristine Zøylner Rubeck INTRA- AND INTER-OBSERVATORY VARIATION OF THYROID SHEAR WAVE ELASTOGRAPHY - A VARIABILITY STUDY

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**Objectives:** The main goal when diagnosing thyroid nodules is to differentiate the few malignant from the overwhelming background of benign lesion. Currently available pre-operative tests are unable to rule out malignancy in a subset of patients, thus making diagnostic surgery necessary. Thyroid nodules constitute a diagnostic challenge subject to continuous research worldwide, and novel biochemical, genetic, radiological, and cytological tools have been suggested in an attempt to limit diagnostic thyroid surgery.

**Aim:** The aim of the study is to evaluate the reproducibility of ultra-sonographic Shear Wave Elastography (SWE) as a novel tool for pre-operative evaluation of thyroid nodules. Hereby, we hope to contribute to a more restrictive approach when selecting patients for diagnostic thyroid surgery.

**Methods:** SWE assesses tissue elasticity in a quantitative manner, depicting findings as a definite variable (Elasticity Index, EI) guided by a color-coded map. The inter- and intra-observer and day-to-day variation of thyroid SWE will be evaluated prospectively by inclusion of 50 patients with thyroid nodules. All SWE examinations will be performed by two blinded and independent operators during an 18 months period.

**Results:** Inclusion is ongoing, and preliminary results will be presented at PhD Day 2015 at Aarhus University.

**Conclusions:** Studies have proposed a potential role of thyroid SWE in the differentiation between malignant and benign nodules, as a higher EI has been described in malignant lesions. The method is time-efficient and easily performed, allowing it to be implemented clinically. However, as the diagnostic accuracy of SWE is not clear, more studies are needed.

P19.06      Christian F. P. Scholz      GENOME-WIDE ANALYSIS REVEALS OPTIMAL SINGLE LOCUS TYPING SCHEME FOR *P. ACNES*

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**Objectives:** To find a cheaper and faster alternative to the existing MLST schemes used for *Propionibacterium acnes* that can be applied in meta-genomic studies.

**Methods:** A reference tree based on 2 Mbp core sequences from 86 *P.*

acnes genomes was used as the golden standard. Using the tree, we defined requirements for an optimal typing scheme. The 86 genomes were aligned with blastn in segments of 500 bp starting from every base position across the entire genome. Using a Python script, each of these segments was evaluated for their use in a single-locus sequence typing (SLST) scheme and compared to the defined requirements.

Results: Our method resulted in a new SLST scheme for *P. acnes*. Compared to existing MLST schemes, it is simpler and cheaper to perform while it retains a high resolution. As a proof of concept, we applied the SLST scheme in a pyrosequencing approach to map the *P. acnes* diversity of facial skin sites and the oral mucosa. It demonstrated symmetric distributions of numerous types between similar sampling sites, and oral-specific sequence types of *P. acnes*.

Conclusion: A SLST scheme for *P. acnes* was developed using a genome-wide mining approach. It has a comparable discriminatory power to existing MLST schemes, and is applicable for population analyses of *P. acnes* in complex microbiotas.

Perspectives: The presented method of identifying optimal SLST candidates may be applied to any bacterial species with a clonal population structure. This strategy could speed up bacterial typing, in particular of mixed communities in complex samples.

P19.07      Mette Nygaard TRACHEOMALACIA DIAGNOSED BY MULTIDETECTOR COMPUTED  
Christensen      TOMOGRAPHY: AN EVALUATION OF DIFFERENT IMAGE ANALYSIS

*M.N. C*

Department of Respiratory Diseases and Allergy, Aarhus University Hospital

Introduction: The symptoms of tracheomalacia (TM) are cough, dyspnea and recurrent infections making it difficult to separate the disease from more common lung diseases. The gold standard for diagnosing TM is by bronchoscopy. After the introduction of multidetector computed tomography, it is clear that TM is more frequent than previously expected. The diagnostic criteria for TM with MD-CT are still unsolved. We here evaluate four methods for diagnosing TM using MD-CT images.

Methods: 374 consecutive HRCT scans performed in full inspiration and in end-expiration were analyzed. Image evaluation was performed in four different ways. The following locations or regions were used for determination of the degree of collapse: A) one cm above the carina, B) the location with maximal collapse was then chosen, C) the entire region from the carina to the thoracic inlet and D) the trachea and bronchial region as defined by the software. The Spearman's correlation coefficient was used to evaluate correlation between the different methods.

Results: The strongest correlation was found between method C (sum of manually measured areas) and method D (volumes generated by the software) with a correlation coefficient  $R=0.877$  ( $p<0.001$ ), but all four methods were comparable with a highly significant correlation coefficient

of 0.767-0.877.

Conclusion: Four methods for diagnosing TM using MDCT scanning were evaluated and were found equally suited. There was a tendency for TM to be more prevalent in older and more obese patients. We recommend using the volumes generated by the software whenever the automatic lung segmentation is performed properly as it is independent of inter-individual variation.

P19.08      Nina Viskum      ASTMAVEN - INCREASED VENTILATION IN HOMES OF ASTHMATIC  
                 Hogaard      CHILDREN: AN INTERVENTION STUDY

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Background: House dust mite (HDM) allergy is a frequent cause of allergic asthma among children. Spending much time indoors, children are exposed to many different indoor air pollutants. Children with asthma and HDM allergy are especially sensitive to these. Reducing the exposure may improve asthma control in these children. Results from previous studies are conflicting.

Objective: We aim at investigating whether an increased ventilation rate is capable of improving indoor air quality and thereby improve asthma control in children with house dust mite allergy and asthma.

Materials and methods: The study is a randomized, double-blind, placebo-controlled intervention study, including 60 children with verified asthma, requiring a minimum of 400 µg of inhaled steroid daily (equivalent to Budesonid). They must have verified HDM allergy and be exposed to HDM allergen in their bed. They must have no other clinically relevant allergies.

The children are randomized into two groups receiving either active ventilation or placebo. The intervention is balanced mechanical ventilation, through 9 months, providing 2-3 airchanges/h in the child's bedroom in active ventilation mode. We monitor indoor air quality and health outcomes every three months. Primary outcome is minimal effective dose of inhaled steroid.

Perspectives: Asthma patients and their families rely on good evidence-based advice on behavior and design of housing, so that the pollutants in the indoor environment that trigger the disease are controlled as well as possible. The results of this project will contribute to the recommendations that can be given in relation to this matter.

P19.09      Mette Sørensen SHARED CARE AND IMPLEMENTATION OF A PEDIATRIC ASTHMA CLINICAL

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**Background:** In the present population-based intervention study, we implemented international asthma guidelines at one hospital and affiliated general practitioners (GPs). Our hypothesis is that implementation can improve intersectional collaboration between physicians based on shared responsibility/Shared Care.

**Material and methods:** The project was carried out at the outpatient clinic at the Paediatrics Department at Viborg Regional Hospital in cooperation with 89 GPs from the Viborg area. The project started in April 2011 and children aged 0-15 years with asthma were identified and followed until fall 2014.

At baseline, 89 GPs validated the diagnosis of asthma in children who had redeemed at least one anti-asthmatic drug prescription (ATC code R03B, R03AC and R03DC) in 2010.

Moreover, we ascertained all hospital outpatient children with an asthma diagnosis (ICD-10 J45.0, J45.1, J45.8, J45.9) from April 2010 till April 2011 (closed/baseline cohort). We did a new search in September 2014 to find new asthma patients in the outpatient clinic during the project period (open cohort).

**Preliminary results:** 81 GPs (91 %) provided data on 1586 children of which 1067 (67 %) had confirmed asthma. In 2012, we received follow-up data on the asthma patients from 67 GPs (75 %). At present, we await new GP follow-up data. At the hospital outpatient clinic, we have established a closed cohort of 481 children and an open cohort of 694 children.

**Perspectives:** In the future, this project will provide documentation for the effectiveness for an asthma quality improvement intervention, which can be used nationally in the future organization of childhood asthma diagnosis, treatment and control.

- P19.10      Camilla Askov      PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)  
Mousing                      WISH TO DISCUSS PALLIATIVE CARE WITH HEALTH PROFESSIONALS

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**Introduction:** Patients with COPD may experience palliative care needs in the early, late, and terminal phases of the disease. Health professionals experience several barriers in their work with identifying, initiating, and evaluating palliative interventions aimed at patients with COPD in primary care. Major barriers to a palliative approach are fear of destroying patients' hopes and difficulties in deciding the right time to initiate discussions about palliative care.

**Aim:** To explore the preferences of home-living patients suffering from COPD in relation to conversations about palliative care needs and interventions.

**Methods:** In the period of 2013-2014, twelve patients diagnosed with COPD were interviewed individually in their homes. The semi-structured interviews were conducted in three homecare districts in Denmark and were analyzed descriptively.

**Results:** Patients reported that they rarely initiated discussions about palliative interventions, as they would not bother the staff with their concerns. Unless they knew the staff very well, they would not open these serious conversations. Several patients explained that they did not discuss their worries with their immediate families either, as they would not cause concern. The analysis showed that patients worry about the future and they would like to discuss: the disease; worries about the future; and management of symptoms with health professionals.

**Conclusion:** Patients expressed that professionals should not be afraid to initiate conversations about palliative care. The patients knew that COPD was a serious illness, and they did not fear that discussions about palliation could destroy their hopes for the future.

P20.01      Lene Duez      ADDED VALUE OF MAGNETOENCEPHALOGRAPHY IN THE DANISH PRESURGICAL EPILEPSY EVALUATION

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<sup>3</sup>Department of Neurology, Aarhus University Hospital, <sup>4</sup>Department of Neurology, Rigshospitalet

**Purpose:** Magnetoencephalography (MEG) is increasingly used in the non-invasive evaluation of patients with refractory focal epilepsy. MEG records the changes in magnetic fields generated by the activity of the neural networks in the brain. EEG and MEG supplement each other in localizing the epileptic focus, because MEG detects epileptic sources tangential to the skull and EEG detects both tangential and radial sources. The magnetic field recorded by MEG is not distorted by the brain, tissue, skull or scalp. This preliminary status of an ongoing project outlines how often interictal

epileptic discharges are detected by MEG or EEG.

Method: MEG (Elekta Neuromag® TRIUX™) 306 channels and simultaneous EEG (60-70 channels) were recorded in 50 consecutive patients with focal epilepsy, referred for epilepsy surgery. Recording duration was one hour in resting conditions, with closed eyes. MEG and simultaneous EEG were manually viewed by skilled personal using CURRY Scan 7 Neuroimaging Suite.

Results: MEG and simultaneous EEG together revealed epileptiform discharges in 68% of the patients. Magnetoencephalography alone revealed epileptiform discharges in 23% of the abnormal MEG/EEG files. Focal discharges were seen in both MEG and in the simultaneous EEG in 71% of the abnormal MEG/EEG files.

Conclusion: MEG detects interictal focal epileptic discharges not captured by conventional EEG. This can lead to a better hypothesis on where to operate. If 3 times repeated EEG including provocation and sleep is normal, MEG could add additional information in the diagnosis and classification of epilepsy.

P20.02      Mikkel Petersen USING MRI BASED TRACTOGRAPHY TO DETERMINE SUBTHALAMIC NUCLEUS CONNECTIVITY IN PARKINSON'S PATIENTS UNDERGOING DEEP BRAIN STIMULATION

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Deep brain stimulation (DBS) is an effective treatment for advanced stages of Parkinson's disease (PD) and other movement disorders such as dystonia and essential tremor. In DBS surgery for PD, an electrode is implanted into the subthalamic nucleus (STN), where it stimulates nearby tissue through electrical impulses. Though an effective treatment, the exact mechanism-of-action of DBS is still poorly understood.

During surgical planning the target location within the STN is based on the visual interpretation of the magnetic resonance images (MRI), combined with landmark anatomy and surgical experience. The STN is known to have three functionally distinct regions (motor, associative and limbic), as established using primate studies. However, these cannot be identified visually and targeted using conventional MRI.

The overall aim of this project is to assess the structural connectivity between the stimulated tissue and cortical regions. This will be achieved non-invasively, using advanced diffusion weighted imaging and probabilistic tractography techniques.

Our immediate aim is to identify regions of the STN showing the strongest connectivity with cortical motor regions. Following this, we aim to combine the tractography-based connectivity measures with CT confirmed locations of the implanted electrodes. This will allow us to examine which fiber tracts are being stimulated by DBS and where they project to in the

brain. Subsequently, correlating clinical outcomes and electrode placement will allow us to evaluate the optimal STN regions to stimulate. This knowledge may potentially assist neurosurgeons in target planning before surgery and optimize long term treatment effect.

P20.03 Kousik Sarathy Sridharan STUDYING SOMATOSENSORY FUNCTION IN PARKINSON'S DISEASE

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Background: Although deep brain stimulation (DBS) of subthalamic nucleus (STN) alleviates motor symptoms and improves quality of life in Parkinson's disease (PD) (1), patients have problems with sensorimotor integration through cortical processing (CP). Somatosensory evoked fields (SSEF) is an effective tool to study sensory CP using magnetoencephalography (MEG)(2).

Methods: 6 PD patients were recruited from the population of STN DBS treated patients at AUH. Clinical interview was conducted and informed consent obtained. MEG-assessments were done OFF medication- ON DBS, OFF medication-OFF DBS for each half hour until 2 hours and then ON medication-OFF DBS. Repetitive median nerve stimulation was performed at 2.5 Hz with an ISI of 350 ms. MaxFilter was used to remove DBS artifacts. Gradiometer pairs showing maximum amplitude and its latency in sensorimotor areas were searched. Repeated-measures ANOVA with a Tukey post-hoc test were performed to determine significant differences in both amplitude and latency.

Results: MaxFilter suppressed the DBS artifacts enabling visualization of SSEF responses. The early responses, namely N20 and P35, were clearly localized in central cortical areas. The SSEF amplitudes and latencies did not significantly differ with DBS therapy or medication.

Discussion: The SSEF did not show any significant variation with therapy. The lack of differences is in congruence with previous studies (3). The mid-latency responses do not seem affected by DBS. It is probable that induced oscillatory activity might contain more useful information.

[1] Just H, Østergaard K; *Mov. Disord.* 2002

[2] Abbruzzese G et.al; *Mov. Disord.* 2003

[3] Airaksinen K et.al; *Hum. Brain. Mapp.* 2011

P20.04 Thorbjørn Søndergaard Engedal THE ROLE OF MICROVASCULAR DYSFUNCTION IN ISCHEMIC STROKE  
*T.S. Engedal*

Center of Functionally Integrative Neuroscience (CFIN), Department of

Background: The spatiotemporal evolution of ischemic stroke is traditionally explained by gradual reductions in cerebral blood flow combined with the detrimental effects of progressive biochemical and molecular disturbances and peri-infarct depolarizations.

Hypothesis: Ischemia has been shown to result in pericyte constriction, edema, dyscoagulation with formation of microthrombi, and inflammation, all of which disturb microvascular flow. The combined effect of these may possibly result in increased capillary transit time heterogeneity (CTTH), which leads to shunting of oxygenized blood through the capillary bed. Thereby ischemia is progressively worsened. Furthermore, baseline chronic and subacute microvascular disease likely augments this effect.

Data: More than 700 prospectively gathered acute ischemic stroke patients from the I-know-stroke database and the Aarhus stroke database are included.

Design: Retrospective database study.

Studies: 1) CTTH map-size predicts final infarct and clinical outcome, 2) CTTH relative to CBF predicts single voxel outcome and 3) Healthy tissue CTTH values are influenced by baseline chronic and subacute disorders.

P20.05 Anna Szyszka DNA METHYLATION OF CACNA1C IN BIPOLAR DISORDER

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Background: CACNA1C, recently identified to be consistently associated with bipolar disorder (BPD) and schizophrenia (SZ), encodes pore-forming unit of the voltage-gated L-type calcium channel, mediating calcium influx upon membrane depolarization, important for proper function of brain and other organs.

Aim: This study investigates differences in DNA methylation of CACNA1C between BPD patients and healthy controls in their blood.

Results and discussion: Investigation of single CpG sites in all CpG islands (CGIs) and one shore of CACNA1C by Sequenom EpiTYPER showed strong similarity in methylation levels between most individuals. Four out of five islands were found to be either fully methylated or fully unmethylated, with one island (CGI 3) showing intermediate methylation level. Closer investigation of DNA methylation at CGI 3, interestingly positioned in the middle of GWAS signal, was performed with iPLEX technology in a larger cohort. We found a significant difference in DNA methylation along this

entire island between cases and controls. Additionally, DNA methylation at CGI 3 was found to be highly correlated with genotypes of the surrounding SNPs previously associated with BPD.

P20.06      Mette Kragh      WAKE AND LIGHT THERAPY TO INPATIENTS WITH MAJOR DEPRESSION - EFFICACY, PREDICTORS AND PATIENT EXPERIENCES

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Background: Patients admitted to a psychiatric hospital with depression are highly tormented and many have suicide thoughts. The treatment in a ward consists of beginning or adjustment of antidepressive medication combined with for instance psychotherapy and exercise offers. Full effect of the treatments is only reached after weeks. Wake therapy is a treatment method which has appeared to reduce depressive symptoms within hours, and in several studies up to 60% of the patients responded to wake therapy. The method consists in the patients staying awake for one night and the following day, in all 36 hours, which is followed by one night of sleep. Light therapy, antidepressants and stabilization of circadian rhythm seem to maintain the effect of wake therapy.

Objective: To examine the efficacy of using wake and light therapy as a supplement to standard treatment of hospitalized patients with depression. Furthermore, the objective is to identify predictors of good effect and to clarify the patients' experiences with wake and light therapy with focus on factors related to the patients' adherence.

Methods: It is a randomized controlled study, and the aim is to include 74 in-patients with major depression. The patients are allocated to standard treatment or to the intervention, which besides standard treatment will consist of three times wake therapy in one week and 30 minutes daily light treatment in the entire nine-week study period. Furthermore, the patients will receive psychoeducation regarding good sleep hygiene and maintaining a stable circadian rhythm. The patients will be requested to keep a diary, and individual semi-structured interviews will be conducted.

P20.07      Rikke Hahn Kofoed      INVESTIGATING A PLK-2 DEPENDENT ALPHA-SYNUCLEIN CATABOLIC PATHWAY

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$\alpha$ -synuclein (AS) is a key molecule in synucleinopathies where it misfolds

and accumulates in degenerating cells. It has been directly linked to the neurodegeneration by duplications and triplications of the gene encoding AS (SNCA) causing familial Parkinson's Disease (PD). Additionally genetic variations in the SNCA causing increased AS levels increase the risk of PD. The level of AS, therefore, seems to play an important role in the development of PD, and it is of great interest to find new ways of decreasing the level of AS.

Polo-like kinase 2 (PLK-2) is involved in neuronal plasticity, regulation of protein levels in post synaptic boutons, and phosphorylation of AS at S129. Moreover, transgenic overexpression of PLK-2 leads to degradation of AS.

Our preliminary data corroborate a role in degradation of AS, as we have seen accumulation of AS in cell lines and primary neurons upon treatment with a PLK-2 specific inhibitor and upon siRNA silencing. Additionally, we see an increase in AS positive structures in cell lines upon PLK-2 inhibition that seems to associate with lysosomes.

We wish to further investigate the PLK-2 dependent catabolic pathway involved in AS degradation using several different techniques.

In cell lines, we will investigate the pathway using microscopy and biochemical methods including different inhibitors and activators of degradative pathways as well as an LC3-mCherry-GFP fusion protein. Additionally, we will search for other proteins phosphorylated by PLK-2 as well as other substrates of the PLK-2 dependent degradative pathway.

P20.08      Marianne von Euler Chelpin      NEUROPROTECTIVE ROLE OF REGULATORY T CELLS IN PARKINSONS DISEASE: EFFECT OF COP-1/ALPHA-SYNUCLEIN VACCINATION ON PATHOLOGY PROGRESSION.

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Parkinson's Disease (PD) is characterized by death of dopaminergic neurons in substantia nigra, resulting in lack of dopamine release in striatum and motor impairment. The remaining neurons present alpha-synuclein (α-syn) intracellular inclusions. Postmortem studies have shown T cell infiltration into the PD brain and vaccination strategies using a wide range of immunogens have shown that the induction of regulatory T cells (Tregs) is protective in PD-animal models. We believe that generation of adequately primed Tregs in the periphery could exert a protective role in the brain. We therefore propose to boost the Treg response as a possible therapeutic approach to induce a tolerant/protective microglia response. We have previously published that low dose α-syn vaccination, ten weeks previous to over expressing α-syn in substantia nigra, reduces protein aggregates in the striatum, induces antibody deposition and permanent Treg infiltration. Using the same PD-model where we unilaterally

overexpress  $\alpha$ -syn in substantia nigra by means of recombinant adeno-associated-viral vectors, we have now tested whether boosting Treg induction with Cop-1, will induce a more robust protection against  $\alpha$ -syn induced pathology. Preliminary results show that the peripheral immune system is modified depending of the vaccine strategy, both in blood and in cervical draining lymph nodes long after vaccination in absence of brain pathology. This correlates to different T cells responses after  $\alpha$ -syn pathology is induced, and results in decrease cell death three weeks post- $\alpha$ -syn induction in substantia nigra.

- P21.01 Noemie Regine Virginie Tentillier ANTI-INFLAMMATORY THERAPY VIA CD163-MACROPHAGES IN THE 6-OHDA PARKINSON'S DISEASE MODEL

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Parkinson's disease (PD) is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra (SN) and the presence in cells of aggregated alpha-synuclein ( $\alpha$ -syn) in Lewy bodies. Among other factors, inflammation seems to play a role in PD neurodegeneration. We have data suggesting infiltration of peripheral immune cells, specifically CD163+ macrophages, into the area of neurodegeneration in the 6-hydroxydopamine (6-OHDA) PD model. We hypothesized that the migration of CD163+ macrophages into the brain-injured area in PD may influence local microglia.

By enhancing M2 profile of peripheral macrophages, these could in turn release anti-inflammatory molecules into the neurodegenerative area modifying local microglia response and resulting in neuroprotection. In a 6-OHDA rat model of PD, designed liposomes targeted for the scavenger receptor CD163 were used to deliver dexamethasone (Dexa) into peripheral macrophages. The liposomes were injected intravenously in a treatment approach, with in parallel 4 control groups. Our data show that liposomes Dexa loaded CD163+ macrophages were able to reach the brain. The treatment modified the peripheral immune system and induced improvement of the motor functions. This paralleled a partial rescue of dopaminergic neurons in the nigro-striatal system. Injection of free Dexa resulted in significant side effects which were not observed in animals treated with Dexa-loaded liposomes. Our data support the modulation of inflammation by targeting macrophages as a putative novel therapy in PD and the use of CD163 targeting a valid and non-invasive approach to modulate neuroinflammation in neurodegenerative diseases.

- P21.02 Erhard Næss-Schmidt MICROSTRUCTURAL CHANGES IN THE BRAIN AFTER CONCUSSION

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Background: More than 20% with concussion present persisting symptoms beyond 3 months. Post-concussion symptoms (PCS) are often diffuse and involve physical, cognitive and emotional domains. Several brain areas have been suggested to be target for injury after concussion. Especially the corpus callosum (CC) and the thalamus (THA) have been areas of interest due to their connection to widespread domains. Whereas conventional MRI lacks the ability to detect tissue pathology in subjects with persisting PCS, MRI methods like Diffusional Kurtosis Imaging (DKI) and Diffusional Tensor Imaging (DTI) are much more sensitive to detect structural changes and might therefore serve as a first indicator of pathology.

Aim: We apply a novel scan protocol with DKI and DTI. It is hypothesized that a group of subjects with persisting PCS will show a difference in the microstructure of the CC and THA compared to controls. The scanning results will be compared with the subjects self-reported PCS and cognitive performance.

Method: 25 subjects with PCS and 25 without PCS, respectively, will be scanned with a conventional MRI protocol including DTI and DKI, 3 months after trauma. The degree of PCS is assessed by the Rivermead post-concussion questionnaire and the cognitive performance by a standardized cognition test battery.

Results: The study can potentially reveal if subjects with PCS have structural brain changes and altered cognitive performance compared to subjects without PCS and - if this is the case - whether they are related.

Perspectives: Sensitive biomarkers are essential to the full understanding of PCS. This study will add further knowledge into the area.

P21.03      Peter Parbo      THE RELATIONSHIP BETWEEN BETA-AMYLOID, TAU AND BRAIN INFLAMMATION IN SUBJECTS AT RISK OF DEVELOPING ALZHEIMER'S DISEASE. A PET STUDY

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Background: Alzheimer's disease (AD) is characterised by abnormal aggregation of beta-amyloid (A $\beta$ ) in extracellular plaques and tau protein in intracellular tangles. These plaques and tangles are accompanied by brain inflammation. We wish to investigate the spatial and temporal relationship between these three pathologies in the development of AD.

Methods: A longitudinal descriptive study using Positron Emission



Tomography (PET) to image A $\beta$ , tau and brain inflammation in healthy controls (HC), mild cognitive impairment (MCI) and early AD. The PET imaging programme comprise  $^{11}\text{C}$ -PiB to image A $\beta$  load,  $^{18}\text{F}$ -T807 to image tau aggregation and  $^{11}\text{C}$ -PK11195 to image activated microglia as a measure of brain inflammation. Along with PET imaging, all subjects will be cognitively assessed using a standard neuropsychometric test battery and have Magnetic Resonance Imaging (MRI). All groups will be assessed at baseline. The MCI cohort will be followed for at least two years, having neuropsychometric testing once a year and after two years they will have the MRI and PET imaging repeated. HC and AD subjects will only be assessed at baseline.

Results: Recruitment was initiated in December 2013. 20 subjects with MCI and 12 HC have been included so far. Preliminary results from the baseline  $^{11}\text{C}$ -PiB PET,  $^{11}\text{C}$ -PK11195 PET and neuropsychometric testing will be presented at the PhD Day on January 23, 2015.

Summary: This study seeks to clarify the role of brain inflammation in A $\beta$  and tau aggregation when subjects are at risk of developing AD. It may help rationalise the use of anti-inflammatory agents as neuroprotective strategies in MCI.

P21.04      Hugo Angleys      THE EFFECTS OF CAPILLARY TRANSIT TIME HETEROGENEITY (CTH) ON BRAIN OXYGENATION

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We recently extended the classical flow-diffusion equation, which is traditionally used to infer brain tissue oxygenation from cerebral blood flow (CBF), to take capillary transit time heterogeneity (CTH) into account. Realizing that cerebral oxygen availability depends both on CBF and on capillary flow patterns, we have speculated that CTH may be actively regulated and that changes in capillary morphology and/or resistance may be involved in the pathogenesis of conditions such as dementia and ischemia-reperfusion injuries.

We critically examined the assumptions involved in the first extended flow-diffusion equation and employed physiologically more realistic descriptions wherever possible. Specifically, we explicitly incorporate the effects of oxygen metabolism on tissue oxygen tension ( $P_{\text{tO}_2}$ ) and extraction efficacy. This is in contrast to the original model, where  $P_{\text{tO}_2}$  was treated as an independent parameter, which was considered to be uniform and constant. Additionally, we assess the extent to which the choice of capillary transit time distribution affects the overall effects of CTH on flow-metabolism coupling reported earlier.

After incorporating tissue oxygen metabolism, our model predicts changes in oxygen consumption ( $\text{CMRO}_2$ ) and  $P_{\text{tO}_2}$  during functional activation in accordance with literature reports. An important prediction is that, for large CTH values, a blood flow increase fails to cause significant improvements

in  $P_tO_2$  and  $CMRO_2$ , and can even lower them; a condition of malignant CTH. These results are found to be largely insensitive to the choice of the transit time distribution, especially when considering physiological values.

- P21.05 Kira Vibe Jespersen MUSIC FOR INSOMNIA - A COCHRANE REVIEW AND META-ANALYSIS

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Insomnia is a common sleep disorder in modern society. It is associated with reduced quality of life and impairments in physical and mental health. Listening to music is widely used as a sleep aid. However, it remains unclear if music listening can actually improve sleep in adults with insomnia. To address this question, we conducted a systematic review and meta-analysis.

Relevant databases were searched without restrictions. We included all randomized controlled trials (RCTs) and quasi-randomized controlled trials (qRCTs) comparing music listening with no treatment or standard care. Two authors independently screened abstracts, selected studies, assessed risk of bias and extracted data from all studies eligible for inclusion. Data on sleep-related outcome measures was subjected to meta-analyses when consistently reported by at least two studies.

Six studies comprising a total of 314 participants were included. The studies examined the effect of listening to pre-recorded music daily between 25 and 60 minutes for a period between three days and five weeks. Five studies reporting outcomes on sleep quality were included in the meta-analysis. The analysis revealed a significant and sizeable main effect ( $Z = 8.77$ ,  $p < .0001$ ; MD: -2.80, 95%CI [-3.42;-2.17],  $k = 5$ ) in favor of the intervention compared to no treatment or treatment as usual.

This systematic review provides evidence that listening to music may improve sleep quality in adults with insomnia. However, more high-quality RCTs are needed, and future studies should consider a wider range of outcomes such as objective measures of sleep and changes in daytime function.

- P21.06 Esben Ahlburg Eickhardt ENRICHMENT ANALYSIS OF GENOMIC FEATURES, TO IDENTIFY GENOME-WIDE PATTERNS OF INSERTIONS/DELETIONS IN CASES OF PSYCHIATRIC DISORDERS FROM THE FAROE ISLANDS

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Though the most common psychiatric disorders have been shown to have high heritabilities (40-80%), little is known about their genetic mechanisms. The genome of individuals with a psychiatric disorder may be enriched with very low-frequency and potentially damaging insertions/deletions (INDELs) and single nucleotide variants (SNVs) that play significant and yet not well investigated roles in the disease heritability. SNVs from several distinct loci have been identified, but these only account for a minor fraction of the heritability. The effects of INDELs remain insufficiently described, though they appear to have a higher inter-individual variability and more severe biological consequences than SNVs, suggesting an important but uncharacterized role in complex traits.

The initial part of the study is build on deep (30x) sequencing data from cases and controls from the Genetic Biobank of the Faroe Islands. Our samples from the Faroese Islands consist of 106 cases with schizophrenia, 28 cases with bipolar disorder and 214 controls. The variants are called using the GATK pipeline and are annotated using a custom script pulling data from the ENSEMBL database.

A total of 259,904 variants have been called using the GATK pipeline. The variant distribution has been characterized in terms of: a) distribution in the genome (what regions/functional elements are affected), b) allele frequencies, c) positions in coding regions, d) distribution across loss of function tolerant genes and e) distribution of INDELs across regulatory regions. We have attempted to identify patterns that might uncover biological characteristics significantly affected in cases compared to in controls.

P21.07      Maria Hønholt Christensen      INNATE IMMUNE EVASION BY THE HERPES SIMPLEX VIRUS -1 PROTEIN ICP27

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An early innate immune response against Herpes simplex virus 1 (HSV-1) is induced via germ-line-encoded pattern recognition receptors (PRR). A central part of the innate response against HSV-1 is the induction of type 1 interferon (IFN), which evokes an antiviral response in virus-infected cells and healthy bystander cells. Nuclear translocation of the transcriptionfactor IRF3 via the STING –TBK1 –IRF3 signaling axis, leads to type 1 IFN expression.

To evade the host-cell immune responses and permit the establishment of lytic infection, HSV-1 express multiple proteins including the essential and

multifunctional protein ICP27. ICP27 is expressed as an immediate early gene, approximately three hours post infection. During the cellular infection, ICP27 shuttles between the nucleus and the cytoplasm, and executes its functions in both compartments.

The ICP27 protein inhibits induction of the type 1 IFN response, but the mechanism is not known. I evaluate in this project, the innate immune inhibition in HSV-1 infected macrophage-like cells (THP-1) and elucidate the mechanism used by ICP27 to inhibit the antiviral response.

It is shown, that THP-1 cells infected with an ICP27 deletion mutant induce higher type 1 IFN and CXCL10 responses on a protein level compared to wildtype HSV-1 stimulated cells, indicating that ICP27 participates in the type 1 IFN inhibition. The ICP27 protein is found to bind specifically to TBK1 and inhibit the translocation of IRF3 to the nucleus. This leads us to speculate, that the ICP27 evasion of type 1 IFN is due to specific TBK1 inhibition.

P21.08      hcbn Nørgaard METABOLIC PROFILES OF 429 PATIENTS WITH SCHIZOPHRENIA AND INCREASED WAIST CIRCUMFERENCE: BASELINE DATA FROM THE CHANGE TRIAL

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Background: People suffering from schizophrenia have a reduced life expectancy, with cardiovascular disease being the major cause of the increased mortality. Antipsychotic treatment, unhealthy lifestyle and insufficient monitoring and treatment of somatic co-morbidity, including risk factors of cardiovascular disease (CVD), have been proposed as potential explanations.

Objective: To describe the proportion of subjects with risk factors above or below clinical recommendations.

Method: Baseline data for 429 patients with schizophrenia and increased waist circumference (WC). For women >88 cm for men >102 cm. Smoking was assessed self reported. We measured lipid profiles, HbA1c and blood pressure. Laboratory tests were non-fasting. Blood pressure was measured 3 times after 5 minutes of rest.

Results: Mean age 38 (SD 12.4). 54% females. WC was 114cm (SD 16.6). 50% were daily smokers. Total cholesterol: 50% >5 LDL: 53% > 3.0, HDL: 56% <1.2. From the cohort 13.5% was diagnosed with type 2 diabetes and 0.5% with type 1. 9.7% had HbA1c >7.3 14% had systolic blood pressure>140 mm hg. 17.4 % was treated with a cholesterol lowering drug. 9.14% was treated with an antihypertensive drug.

Conclusion: The alarmingly high proportion of subjects suffering from metabolic disturbances call for immediate action regarding primary and secondary prevention of CVD in people with schizophrenia. It is important with an increased attention on the somatic co morbidities in this group of

vulnerable patients. Further research should investigate if primary care can be better integrated in the care of this population.

P21.09      Alyssa Huebner      DEVELOPING PLURIPOTENT STEM CELLS AS MODELS FOR STUDYING PARKINSON'S DISEASE IN VITRO

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Parkinson's disease (PD) is a neurodegenerative disorder that is characterised by motor impairment resulting from the gradual loss of dopaminergic neurons within the substantia nigra. The development of new drugs from animal models to treat PD has been challenging, with a substantial percentage failing in human clinical trials. New human models of PD may help overcome this translational limitation with reprogrammed human pluripotent stem cells (hPSCs) offering a potential source of clinically relevant cells. The aim of this project is to generate hPSCs from PD patients carrying a GBA1 mutation, a familial form that closely resembles sporadic PD, which will be used to generate dopaminergic neurons to model PD in vitro. Using new gene editing techniques the GBA1 mutation will be corrected to generate isogenic controls and both PD and isogenic cell lines will be analysed for pathological differences. The overall goal is to use this in vitro system to uncover potential new drug targets.

P21.10      Zongpei Zhao      STRUCTURE OF A NEURONAL PROTEIN COMPLEX INVOLVED IN NEURODEGENERATIVE DISEASE

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Macromolecular complexes are essential for cell function. Typically, these macromolecular complexes are composed of multiple proteins and/or nucleic acids. Alteration of these complexes caused by e.g. inherited mutations can severely affect the cell function. In case of neurons, this can result in progressive neurodegeneration. In order to provide insights into the structural organization of a protein complex important for neuronal function, we subclone and express the respective proteins and protein fragments in different host cells. In particular, we wish to study the domain architecture and structural organization of the neuronal macromolecular complex in its wildtype and mutant form. To this end, we express smaller protein fragments in an E. coli overexpression system. In contrast, larger human proteins are difficult to express in E. coli. Therefore, we selected an insect cell expression system suitable for co-expression of complex and large proteins. The purified proteins and protein fragments will be used to reconstitute and analyze the protein complexes in a stepwise approach.

Specifically, we will use biochemical and structural approaches. Together, these studies will provide insights in the structural organization of the neuronal protein complex in health and disease and will thus add to the understanding of the cellular function of the macromolecular complex in healthy and diseased neurons.

P22.01      Amanda Eskelund      ALTERED TRYPTOPHAN METABOLISM IN A GENETIC RAT MODEL OF DEPRESSION

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Depression is a highly prevalent disease with heterogenous symptoms and subsequently, the pathomechanisms difficult to unravel. Several studies have previously linked depression to changes in tryptophan metabolites (TRYMETs) including serotonergic and glutamatergic dysregulation to stress- and inflammation-induced depression. However, these studies have often focused on a subset of metabolites where a larger picture could provide valuable information on the underlying pathophysiology. Thus, we sought to map 13 TRYMETs, encompassing both the serotonergic and kynurenine pathways, in our rodent, genetic model of depression using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Female, 12-20 weeks old, depressive-like flinders sensitive line (FSL) (n=28) and their counter-part control flinders resistant line (FRL) rats (n=32) were subjected to forced swim (FST) and subsequently euthanized to collect plasma and both left- and right-side hemispheres, including cerebellum. Along with higher immobility of the FSL rat, we found increased levels of the potential neurotoxin, 3-hydroxykynurenine (3HK), and lower levels of both anthranilic acid (AA) and 5-hydroxytryptophan (5HTP) in the brain as compared to the FRL rat (p<0.001). In plasma, 5-hydroxyindoleacetic acid (5HIAA) was higher in the FSL rats, where as picolinic acid, AA and quinolinic acid concentrations were lower as compared to the control FRL rats (p<0.0001). There were no hemisphere-differences in TRYMETs. Thus, this study suggests that the interplay of both kynurenine and serotonergic pathway metabolites could be involved in the depressive-like phenotype of FSL rats.

P22.02      Mads Engel Hauberg      DISSECTING THE ROLE OF MICRORNAS IN THE ETIOLOGY OF SCHIZOPHRENIA

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Recently, the largest genome-wide association study (GWAS) for schizophrenia to date identified 108 associated loci. Despite this advancement, the genetic mechanisms underlying the disorder are poorly understood. In an attempt to mitigate this problem, we looked at multiple levels for involvement of miRNA in the etiology of schizophrenia using data from the aforementioned study. We identified an overall enrichment of miRNA binding sites in genes associated with schizophrenia. We then conducted gene set analyses for all conserved miRNA families to test whether a set of predicted targets of a miRNA family was significantly associated with schizophrenia, and found the miR-9-5p targets to be the most strongly associated gene set. This finding is of particular interest as miR-9-5p is involved in neuronal differentiation, has a regulatory loop with FXR1, and regulates dopamine D2 receptor density. We next tested miRNA located in the 108 schizophrenia-associated loci (which cover FXR1 and DRD2) or in schizophrenia-associated CNVs. In these analyses, miR-185-5p, which is located in the 22q11.21 CNV region, showed evidence of association. Finally, we looked for functional SNPs in miRNA genes and their promoters, eQTLs changing miRNA expression, and SNPs altering miRNA-binding sites. Notably, we identified a potentially functional genome-wide significant SNP in a predicted promoter of miR-137 and one changing the target site of miR-1/206/613 in NT5C2. Our study clearly indicates an involvement of miRNA in the etiology of schizophrenia.

P22.03 Kristian  
Lundsgaard  
Kraglund

#### PLATELETS & SEROTONIN

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Purpose: To examine the effects of selective serotonin reuptake inhibitor (SSRI) treatment on platelet reactivity and platelet turnover.

Theoretical background: Most of the body's serotonin (~95%) resides in the gut and is synthesized within the bowel, by the enterochromaffin cell (EC). Secretion overflow reaches the blood where almost all serotonin is transported in dense granules by platelets. These cells are anucleated and thus unable to synthesize serotonin, but can take up the amine avidly from plasma through the serotonin reuptake transporter - the principal action site of the inhibiting SSRI. Serotonin is secreted by the platelet dense granules during platelet activation and plays a role in promoting platelet aggregation and vasoconstriction of surrounding blood vessels, facilitating haemostasis. Serotonin is considered a relatively weak platelet activator, but it greatly potentiates the aggregation induced by i.a. adenosine diphosphate (ADP). All SSRIs have shown to produce a drastic decrease (80-90%) in platelet serotonin content. If serotonin stored in platelets plays a role in haemostasis, it follows that a drastic depletion induced by SSRIs should have a biological and clinical impact.

Study design: Patients are recruited from the TALOS-trial (citalopram or placebo). Platelet reactivity is tested during and 14 days after final dosage

project medication treatment, using i.a. the VerifyNow System (ADP). n=60.

Outcome: Platelet reactivity and turnover through Platelet Reactivity Unit (PRU), immature platelet fraction and complete platelet count and possible soluble p-selectin.

- P22.04      Martin      EXTRACELLULAR  $Mg^{2+}$  AND  $Ca^{2+}$  REDUCE MYOTONIA IN CLC-1 INHIBITED  
Brandhøj Skov      ISOLATED HUMAN MUSCLE

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Myotonia congenita is an inherited neuromuscular disorder characterized by spontaneous muscle excitations and delayed relaxation of skeletal muscle. The disorder is caused by loss-of-function mutations in the gene encoding the CLC-1 channel. Large variation is observed between patients suffering from this disease, and family members with identical mutations can experience markedly different degrees of myotonic symptoms. In addition, patients experience day-to-day variation of their symptoms that may not be explained by variation in genotype. This suggests that factors other than genomic contribute to the severity of symptoms. We have shown that one such factor may be the extracellular concentration of  $Mg^{2+}$  and/or  $Ca^{2+}$  experienced by the muscle. In two studies, we investigated the effect of extracellular  $Mg^{2+}$  and  $Ca^{2+}$  on pharmacologically induced myotonia in isolated rat and human skeletal muscle. In both studies, we found an inverse relationship between the concentration of  $Mg^{2+}$  and/or  $Ca^{2+}$  and myotonic contractions. The relationship between the concentration of divalent cations and myotonic contractions was present within the narrow physiological concentration ranges of both ions. We found that as little as 100  $\mu M$  difference in the concentration of either ion may significantly impact myotonic contraction in vitro. Furthermore, we found that the two ions may substitute one another implying that a common mechanism may be shared by the ions. However, we have not yet determined the mechanism behind this phenomenon, but it is possibly due to an effect on the voltage sensitivity of the  $Na_v1.4$  sodium channel.

- P22.05      Arnela      SORLA'S INFLUENCE ON RETINAL APP PROCESSING  
Mehmedbasic

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Alzheimer's disease is a progressive neurodegenerative disorder and the most common form of age related dementia. A main pathological hallmark is the extracellular accumulation of A $\beta$  peptides in the brain, which originates from proteolytic processing of the Amyloid Precursor Protein (APP). Although the brain is the most common manifestation site of



the disease, increasing evidence shows that the eye, especially the retina, is also affected.

SorLA is a mosaic membrane protein belonging to the Vacuolar protein sorting 10 protein (Vps10p) receptor family, which also includes Sortilin and SorCS1-3. It is expressed abundantly in the brain, but also in other tissues such as spinal cord, liver, adrenal glands and testis. Its expression levels in the eye and the retina are yet unknown. SorLA is genetically linked to Late Onset Alzheimer's Disease (LOAD), and patients suffering from LOAD have decreased sorLA expression in the brain.

Several studies have shown that sorLA interacts directly with APP and regulates APP intracellular sorting, leading to a reduced processing of APP and thereby decreased A $\beta$  generation. It is yet unknown if sorLA exhibits this protection in the retina as well. If sorLA exhibits the same effect on APP in the retina as in the brain, then the decrease in sorLA levels in the brain of LOAD patients would possibly be mirrored in the eye, making sorLA in the eye a potential biomarker for LOAD.

We have sorLA<sup>-/-</sup> mice which are viable and do not exhibit any visible abnormalities. In this study, we analyzed the expression levels of sorLA in the retina and investigated sorLA's effect on APP processing in the murine wt and sorLA<sup>-/-</sup> retinas.

P22.06      Anders      PROBIOTIC TREATMENT HAS ANTI-DEPRESSANT EFFECT INDEPENDENT OF  
Abildgaard      DIET

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The literature suggests a bi-directional association between metabolic disorders (type 2-diabetes, metabolic syndrome) and depressive disorder. The gut microbiota may play an important role in both disease entities, and diet is known to alter the gut microbiota composition.

The study aimed at examining whether probiotic treatment would affect glucose metabolism or depressive-like behaviour in healthy rats, and whether probiotic treatment could protect against the adverse effects of a high-fat diet.

40 male Sprague-Dawley rats were fed a high-fat or control diet for 10 weeks. Additionally, a probiotic mix (8 lactobacillus/bifidobacteria species) or placebo was administered daily during the last 5 weeks. The animals were subjected to behavioural as well as metabolic tests. Furthermore, qPCR was done on selected brain areas, and cytokine production from anti-CD3/28 stimulated blood lymphocytes was measured.

Independent of diet, probiotic treatment was associated with a marked reduction in depressive-like behaviour. Consumption of high-fat diet led to

increased body weight as well as increased plasma glucose, insulin and endotoxin levels, but probiotic treatment did not affect these measures. Diet and probiotics were associated with complex changes in mRNA levels of neurotrophic and HPA axis regulating factors.

Our findings add perspectives to the potentially important role of the gut-brain axis and clearly support the novel concept of "psychobiotics". Indeed, the probiotics used in this study should also be validated in a depression model. Nevertheless, our study lends inspiration to further studies into the involved pathophysiological mechanisms.

P22.07      Ali Khalidan      PRECLINICAL IN-VIVO IMAGING OF ACTIVATED NMDA RECEPTOR ION  
Vibholm      CHANNELS WITH THE NOVEL RADIOLIGAND  $^{18}\text{F}$ -GE179

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Background: NMDA receptor ion channels (NMDAr-IC) play a key role in neuronal connectivity. Overactive NMDAr-IC may result in neuronal epileptogenesis and seizure. Localising an epileptic focus in patients with refractory epilepsy can be difficult and imprecise. Non-invasive detection of overactive NMDAr-IC would be valuable in the pre-surgical evaluation. Imaging with Positron Emission Tomography (PET), using the novel radioligand  $^{18}\text{F}$ -GE179, which selectively binds to NMDAr-IC, may lead to better detection and understanding of altered NMDAr-IC.

Purpose: Validation of  $^{18}\text{F}$ -GE179 in rat and pig models of brain stimulation as a prelude to studies in epileptic patients.

Objective: Induce lateralised NMDAr-IC activation by repetitive unilateral stimulation in rats and Deep Brain Stimulation (DBS) in pigs and image the activation with  $^{18}\text{F}$ -GE179.

Methods: Stereotactic surgery with electrode implantation in the right hippocampus of 21 rats and implantation of DBS electrode in the right hippocampus of 4 mini-pigs. Repetitive electrical stimulation induced seizures in rats and discharges during DBS in pigs.

Results: Rat scans suggest lateralisation of  $^{18}\text{F}$ -GE179 binding signal in stimulated right hippocampus. Further rat experiments are underway. Preliminary scan results in pig show a lateralised  $^{18}\text{F}$ -GE179 signal induced by DBS in an intensity-dependent manner.

Conclusion: In-vivo PET imaging of activated NMDAr-IC with  $^{18}\text{F}$ -GE179 could be beneficial in the study of refractory focal epilepsy and aid the pre-surgical evaluation of patients. Future studies include  $^{18}\text{F}$ -GE179 PET in patients with refractory epilepsy in order to detect overactive NMDAr-IC and thereby the epileptic focus.

- P22.08 Inga Christensen ATYPICALLY LOCATED PROTEINS IN A NORMALLY POLARIZED EPITHELIUM
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- The choroid plexus epithelium (CPE) is a highly productive cell monolayer that plays a crucial role for cerebrospinal fluid production. The cellular distribution of membrane proteins in the CPE is known to differ from other transporting epithelia, and previous studies has shown luminal localization of the Na<sup>+</sup>,K<sup>+</sup>-ATPase, Na<sup>+</sup>/H<sup>+</sup>exchanger 1 (NHE1) and Na<sup>+</sup>/K<sup>+</sup>/Cl<sup>-</sup> cotransporter 1 (NKCC1) transporter proteins. Their luminal localizations are opposite to every other known epithelium, whereas other proteins, such as AE2 and AQP1, have normal membrane distributions.
- In the current study, we looked further into the polarity of CPE cells, which previously only has been described by observation of macromolecular structures; e.g. tight junctions, microvilli and adherens junctions. The different membrane domains of polarized cells have distinct protein compositions. Well defined groups of the so-called polarity proteins establish and maintain the distinct membrane domains in the polarized epithelial cell. Here, we document the normal polarity of CPE cells through localization of basic polarity proteins in the epithelium; aPKC in the apical membrane domain, PAR-3 at the most apical junction complex and PAR-1 in the basolateral membrane domain.
- The mechanisms behind atypical localization of some transmembrane and cytoskeletal proteins in the CPE - a normally polarized epithelium are unknown, but may be significant for basic epithelial cell biology. Therefore, a more comprehensive analysis of the protein expression and trafficking machinery in the choroid plexus is warranted.
- P22.09 Anders Gunnarsson STEM CELLS IN THE EPIDERMIS: INVESTIGATING THE RELATION BETWEEN GENE EXPRESSION, EPIGENETIC MARKS AND CELL POSITIONING
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- Purpose: Degenerative diseases can be caused by the loss of specific cell types and it is believed that such diseases can be treated using stem cell therapy. A deeper knowledge of what regulates stem cells is crucial in order to select the best population for a therapeutic treatment. The murine and human epidermis contains a number of stem cells, residing at different locations. In mice, the absence of Sca-1 expression has been shown to identify follicle stem cells and will be further analyzed during the project.
- Objectives:
- A) Examine how the keratinocyte stem cell populations in mice and human

epidermis can be described by their epigenetic-, gene expression profiles and by functional assays.

B) Examine how different phases of induced cellular reprogramming affects epigenetic memory.

C) Examine the gene expression profiles in transgenic mice that lack or overexpress Sca-1, and together with functional assays explain the role of Sca-1 in epidermal stem cell fate and epidermal maintenance.

Methods: Transgenic mice will be analyzed, which overexpress or lack Sca-1 in keratinocyte stem cells. Patient abdominal tissues are used for the human stem cell research. Using conjugated antibodies, specific cell type isolation is made by FACS Core Facility AU for subsequent RNA isolation and transcriptome profiling using microarrays. Non-viral and non-integrating episomal plasmids expressing the reprogramming factors Oct4, Sox2, Klf4, L-Myc, Lin28 are used for cellular reprogramming.

P23.01 Le Le

#### STRUCTURAL STUDIES OF PROTEIN COMPLEXES BY MOLECULAR ELECTRON MICROSCOPY

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Multi-protein assemblies constitute an important group of pharmacological target molecules with relevance for public health due to their being the primary targets of many drugs. However, knowledge about the three-dimensional (3D) structures of protein complexes is often limited due to the technical challenges of enriching functional protein complexes in an amount and purity suitable for structure determination. Many available prokaryotic or eukaryotic expression systems are afflicted with technical shortcomings regarding co-expression of multiple proteins, especially when the proteins of interest amount to a total molecular weight of several hundred kilodaltons and represent difficult targets for the cellular translation and folding machinery. Due to recent advances in baculovirus systems, co-expression in insect cells has become a key approach for the investigation of multi-protein complexes. Here we are going to express the constituents of a protein assembly in an insect cell system using recombinant baculovirus with the aim to purify and reconstitute the protein complex. This approach will ultimately allow determining the overall structure of the protein complex using electron microscopy (EM) combined with single-particle image processing.

P23.02 Toke Jost  
Isaksen

#### UNDERSTANDING THE PATHOLOGY OF ALTERNATING HEMIPLEGIA OF CHILDHOOD USING KNOCK-IN MICE

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Alternating hemiplegia of childhood (AHC) is a rare neurological disorder caused by de novo mutations in the ATP1A3 gene encoding the  $\alpha_3$  subunit of the  $\text{Na}^+/\text{K}^+$  pump. The  $\text{Na}^+/\text{K}^+$  pump is a transmembrane-located ion pump that actively transports sodium and potassium by hydrolysis of ATP. The pump consists of a catalytic  $\alpha$  subunit and regulatory  $\beta$  subunit. Four different  $\alpha$  subunits are found in mammals,  $\alpha_3$  is mainly expressed in neurons in the central nervous system. AHC develops in early childhood and causes severe neurological and developmental impairments. Major symptoms include hemiplegia, dystonia, ataxia and epileptic seizures.

The aim of this study is to analyse the pathology of AHC, with focus on motor and cerebellar function, using the heterozygous knock-in mouse line  $\alpha_3^{+/D801Y}$  harbouring the D801Y in vivo-relevant disease-mutation.

Homozygous  $\alpha_3^{D801Y/D801Y}$  mice die shortly after birth, whereas heterozygous  $\alpha_3^{+/D801Y}$  mice can survive but are still less viable compared to  $\alpha_3^{+/+}$  wild type (WT) littermates. Reduced  $\alpha_3$  protein levels were found in brain lysates from  $\alpha_3^{+/D801Y}$  mice,  $\alpha_1$  protein levels were contrary higher in  $\alpha_3^{+/D801Y}$  mice. Motor and movement function has been assessed using motor-related behavioural tests. The  $\alpha_3^{+/D801Y}$  mice showed severe ataxia, with significant more slips during balance beam test and longer time to climb in rope climbing test compared to WT littermates. Mild stress induced hemiplegia/dystonia and seizures in  $\alpha_3^{+/D801Y}$  mice.

In conclusion, the  $\alpha_3^{+/D801Y}$  mice phenocopy ataxia and many other symptoms of AHC patients (Holm et al, unpublished) and will hopefully help to improve the treatments available to AHC patients.

P23.03

#### DYNAMIC CONTRAST-ENHANCED CT IN THE FOLLOW-UP OF IMAGE-GUIDED LIVER INTERVENTIONS

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Background: Follow-up image evaluation is inadequate at detecting recurrence after image-guided interventional procedures of liver metastases from colorectal cancer (CRC).

Dynamic contrast-enhanced computed tomography (DCE-CT) is based on repetitive scans following contrast media injection. A time-attenuation curve is created from which the following parameters can be calculated: Perfusion, Blood Volume, Mean Transit Time and Permeability.

Aim: To investigate whether DCE-CT is more effective than routine contrast-enhanced CT at detecting recurrence following local treatments

of colorectal liver metastases.

Method: The project is designed as two prospective comparative cohort studies in patients with liver metastases from CRC receiving:

1. Radio-Frequency-Ablation (RFA): Minimally invasive treatment with image-guided (Ultrasound or CT) placement of a needle electrode in the tumor. High-frequency electrical currents are passed through the electrode destroying the abnormal cells.

2. Drug-Eluting-Beads-Irinotecan-TransArteriel ChemoEmbolization (DEBIRI-TACE): Microspheres loaded with Irinotecan chemotherapy are placed directly into the tumor tissue using a microcatheter. Microspheres imbedded into the tissue cause stasis and a highly localized concentration of chemotherapy within the tumor itself.

DCE-CT scans will be performed at baseline (before treatment) and follow-up at months 1, 4 and 8. These scans will be analyzed, and the resulting parameters will be correlated with time to recurrence on a per-lesion basis.

Perspectives: We believe that DCE-CT detects recurrence earlier than conventional imaging allowing for further treatment and a better prognosis.

P23.04 Gudrun  
Winther

MATERNAL PERINATAL HIGH-FAT DIET INCREASES ANXIETY-LIKE  
BEHAVIOR IN OFFSPRING

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Background: Maternal obesity during gestation represents a significant health risk for the offspring. This becomes evident later in life and includes metabolic syndrome, cardiovascular disease and affective disorders. Inflammation has recently been shown to play an important role in the pathophysiology of affective disorders. Systemic inflammation is a hallmark consequence of a high-fat diet and maternal obesity may lead to fetal inflammatory responses. Therefore, we hypothesize that an altered immune response could be responsible for the metabolic and psychiatric symptoms in the offspring.

Objective: The objective of this study was to investigate the influence of a high-fat diet on the affective-like behavior in the offspring.

Methods: Age matched female rats (Sprague Dawley, n=20) were fed a high-fat diet or a control diet 8 weeks before breeding, and continued on this diet throughout gestation and lactation. Male and female offspring were tested at the age of PND56 in different behavioral settings. Plasma cytokines were determined by Luminex liquid array-based multiplexed immunoassays.

Results: After 8 weeks on the obesogenic diet, female rats had a

significantly higher intake (Kcal) than control dams. Offspring from high fat fed rats were significantly heavier than control offspring at weaning. Offspring exposed to perinatal high-fat showed increased time spent in the closed arm in the elevated plus-maze indicating anxiety-like behavior.

Conclusion: The data strongly suggest that that dietary environment during development contributes to behavioral consequences. This effect seems to be specific for anxiety-like behavior.

P23.05 Maj Ulrichsen SORTILINS IN PERIPHERAL NERVE REGENERATION

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Physical injury to peripheral nerves is the most common cause of peripheral neuropathy. Although peripheral nerve fibers retain a capacity for regeneration, functional recovery is often poor and rarely reaches the pre-injury level.

Recent data imply important functions of sortilin and SorCS2 in the peripheral nervous system and following peripheral nerve injury (PNI). Sortilin and SorCS2 interact with and facilitate anterograde axonal transport of Trk receptors, hereby enhancing signaling by neurotrophins (NT) and mediating NT-induced neuronal survival, growth and differentiation. Accordingly, inhibition of sortilin and/or SorCS2 suppresses development of neuropathic pain following PNI, presumably by impairing NT signaling in spinal cord dorsal horn. Furthermore, we observe that PNI dramatically increases the expression levels of SorCS2 in Schwann cells, as do expression of p75<sup>NTR</sup> and proBDNF and -NGF. Interestingly, sortilin and SorCS2 is known to induce NT-mediated neuronal apoptosis when engaging in complex formation with p75<sup>NTR</sup> and pro-NTs.

As the Sortilins are strongly linked to NT signaling, and NTs and their receptors are involved in regenerative processes in both neurons and Schwann cells, we hypothesize a role of sortilin and SorCS2 in regeneration following peripheral nerve injury. Currently, the Sortilin expression profile of subpopulations of dorsal root ganglia (DRG) neurons and cultured Schwann cells are being established and it is being investigated how the Sortilins are regulated in DRG and sciatic nerve following PNI, as up- or down-regulation of the Sortilins might be important for successful peripheral nerve regeneration following injury.

P23.06 Ardis IMPLICIT AND EXPLICIT SOCIAL INFLUENCE ON DECISION-MAKING IN  
Simonsen SCHIZOPHRENIA

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**Background:** Social norms are crucial in shaping behavior such as enacting social roles. Individuals with schizophrenia show severe impairments in fulfilling such social roles. These impairments are strongly related to deficits in social cognition, i.e. the detection, processing, and use of social information. However, few studies have investigated whether patients with schizophrenia show a reduced tendency to conform to social norms when making decisions and if so whether this is due to differences in implicit or explicit processing of social norms.

**Methods:** We used two tasks to assess the tendency to conform to social norms when making decisions. In the implicit influence task, we assessed the subjects' tendency to be incidentally influenced by previously shown opinions of others when assessing the trustworthiness of human faces. In the explicit influence task, we assessed the subjects' tendency to copy other people's decision when judging a future outcome. The study included 39 patients with schizophrenia and 40 matched controls.

**Results:** Compared to controls, patients showed an increased tendency to conform to implicit social influence on trustworthiness judgments. However, they tended to ignore other people's judgment (explicit social influence) when making decisions about a future outcome even when the others were a majority and provided useful information about the outcome.

**Conclusions:** The findings indicate that patients with schizophrenia are reluctant to use explicitly processed information to shape their behavior to fit social norms, while use of implicitly processed information seems exaggerated.

P23.07 Michael  
Aagaard  
Andersen

LOSS OF LEUCINE-RICH-REPEAT-KINASE-2 REVERSES INCREASED  
IRREGULARITY FIRING IN SUBTHALAMIC NUCLEUS INDUCED BY VIRAL  
OVEREXPRESSION OF  $\alpha$ -SYNUCLEIN IN VIVO

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Parkinson's disease is the 2<sup>nd</sup> most common neurodegenerative disorder affecting 1-2% > the age of 60. Mutations in leucine-rich-repeats-kinase-2 (LRRK2) are the most common cause of genetic linked PD. Amongst those, the G2019S-LRRK2 mutation leads to changes in LRRK2 kinase function which is considered critical in PD aetiology. Another hallmark of PD is represented by the presence of Lewy bodies throughout the brain and other organs. The main component of Lewy bodies is  $\alpha$ -synuclein ( $\alpha$ -syn). Interestingly, there is increasing evidence that LRRK2 and  $\alpha$ -syn may share common pathophysiological mechanisms in PD.

In the present thesis, we used of a proposed rat model of PD based on intracerebral injection of a viral vector to overexpress hwt- $\alpha$ -synuclein. This model has earlier shown electrophysiological alterations similar to those



reported in humans suffering of PD. To investigate a putative interplay between LRRK2 and  $\alpha$ -syn in PD, overexpression of hwt- $\alpha$ -syn was induced in LRRK2 KO rats and their control wild-type rats. We show that LRRK2 KO has a protective effect against electrophysiological changes in STN caused by overexpression of  $\alpha$ -synuclein. However, LRRK2 KO does not significantly change the behavioural or biochemical (e.g. loss of tyrosine hydroxylase in STR) effects of viral overexpression of  $\alpha$ -synuclein. Interestingly, preliminary data suggests that the protective effect is correlated with decreased phosphorylation of  $\alpha$ -synuclein in the LRRK2 KO.

KO of LRRK2 has a partially protective effect against pathophysiological changes induced by viral overexpression of  $\alpha$ -synuclein. In this perspective, inhibition of LRRK2 in CNS may present a viable target for PD treatment.

P23.08      Sakthidasan      TOWARDS CHARACTERIZING A MACROMOLECULAR COMPLEX  
Jayaprakash      INVOLVED IN CONTROLLING NEURONAL DIFFERENTIATION

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During development, the expression of genes specific for differentiated, mature cells must be repressed in stem cells and progenitor cells, and only be activated once a cell differentiates towards to a mature cell. In contrast, an aberrant expression of genes controlling cell development can contribute to severe diseases such as malignant brain cancer. Proteins involved in transcriptional repression assemble into multi subunit protein complexes. In this PhD project, we amplify the respective genes of the transcriptional repressor from cDNA libraries. The amplified genes are then cloned into a pUC57 vector. Once established, we also subclone the genes into a special vector for yeast two hybrid screening, the Dualhunter system, which is especially suited for transcription factors and other nuclear proteins. Putative interaction partners will be verified by GST pull-down assays. Moreover, we wish to express the transcriptional repressor complex in the MultiBac system, which allows the expression of eukaryotic multi protein complexes in insect cells. Of note, proteins can undergo post translational modifications in the insect cells. To this end, multiple numbers of genes will be cloned into a single expression vector for the multiprotein production. The selection of genes into a single multigene cassette is based on the result of interaction partner screens as established by the yeast two hybrid screening. Structure determination by using electron microscopy in relation to the function of the macromolecular complex will provide insights into the molecular mechanism of the transcriptional repressor complex.

P23.09      Ali H. Rafati      SPATIAL DISTRIBUTION OF NEURONS IN LAYER-III OF MEDIAL PREFRONTAL  
CORTEX OF FLINDERS RATS WITH MATERNAL SEPARATION

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**Background:** The Flinders Sensitive Line (FSL) rat is a genetic animal model of depression, and maternal separation (MS) of rats is an example of early-life adversity which leads to altered corticogenesis and depressive like behaviors. Rat prefrontal cortex is a brain region in which maturation occurs mainly during postnatal period. It has been shown that neurons in different layers of cortex are developed and organized vertically, in columnar-like structures. There is compelling evidence that early life stress can change structure and function of interneurons in medial prefrontal cortex (mPFC) of rats, consequently it is expected that the columnar distribution of ensembles of neurons from layer-II/III in mPFC might be affected. To test this hypothesis, we aimed to find differential degree of columnarity in layer-III of mPFC from the Flinders rat (FSL/FRL) and its environmental interaction, superimposed stress of maternal separation.

**Material and method:** In this study, we used coronally-sliced thick plastic sections to record the spatial position of neurons contained in two systematically-chosen samples per hemisphere of brain from layer-III of mPFC. Each sample is a well-defined 3-dimensional region containing up to two thousands neurons, the longest axis of the 3-dimensional region is parallel to the mPFC surface. The volume of mPFC and layer-III were obtained by the Cavalieri estimator. The degree of columnarity of spatial arrays of neurons perpendicular to the mPFC surface will be analyzed by applying a new mathematical tool; the Cylinder K-function, recently developed by statistical collaborators in CSGB.

P23.10 Hong Sain Ooi A FRAMEWORK TO EVALUATE THE QUALITY OF PROTEIN INTERACTION NETWORK

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Protein interaction networks have been widely used to assist the interpretation of GWAS results. However, it is well-known that the current collection of protein-protein interaction (PPI) data is far from being complete and contains a huge amount of false-positive interactions. The incompleteness of the PPI data likely reduces the sensitivity of network-

based approaches, while inclusion of false-positive interactions might lead to wrong conclusions. Several scoring functions have been proposed to evaluate the reliability of PPI, yet the correlations between their conclusions remain low. Thus, it seems to be of utmost importance to characterize and evaluate the quality of the PPI data prior to using them to assist the interpretation of GWAS results.

We have developed a framework to evaluate and characterize PPI databases. Our result suggested that the choice of scoring function and subsequently the content of the PPI databases generally reflect both the needs with regards to specific research questions asked and the authors' beliefs in what contributes to the reliability of an interaction. While we acknowledge that these circumstances might not correlate well with our choice of the golden positive set, we would like to point out that our choice for the golden set is based on the assumption that two interacting proteins are involved in the same biological process. Thus, we believe that it should be a good estimator for the reliability of a scoring function for a particular protein interaction network.

P24.01      Esben Nielsen    FUCHS ENDOTHELIAL DYSTROPHY: CLINICAL CHARACTERISTICS, TREATMENT OUTCOME, AND PATHOLOGY

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Background: Fuchs' endothelial dystrophy (FED) is a corneal eye disease, which causes poor vision. FED is treated by corneal transplantation. We are conducting a study that in part aims to investigate the ability of the transplanted graft to control oedema.

Materials and methods: Sixteen FED patients were compared to 10 age-matched normal controls. Corneal oedema was induced with a contact lens, and we studied the increase and decline in corneal thickness. We compared per cent of swelling induced (%SI) by unpaired t-tests, and analysed deswelling curves using nonlinear regression and sum-of-squares F-tests.

Results: %SI was similar between groups ( $p=0.20$ ). The deswelling curves exhibited exponential decay properties for both groups. During the first hour after contact lens removal, the deswelling was similar between the groups ( $p=0.8$ ), but after one hour deswelling was slower in the FED group ( $p<0.00001$ ). At the end of the experiment, CCT in the normal corneas was  $-0.8$  mm ( $\pm 2$  mm) from the baseline value, whereas CCT was  $6.8$  mm ( $\pm 10$  mm) from baseline in the FED group ( $p=0.02$ ).

Conclusion: After one hour, deswelling became significantly slower in the FED group and did not return to baseline, which is probably due to lower endothelial pump capacity. In the normal group, we noticed that CCT returned to baseline within 1 mm on average, indicating that corneal hydration is closely regulated under normal circumstances.

- P24.02      Christophe Henri Valdemar Duez      EARLY NEUROLOGICAL PROGNOSTICATION WITH BIOMARKERS OF PATIENTS IN THERAPEUTIC HYPOTHERMIA AFTER CARDIAC ARREST  
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- Introduction: In Denmark, approximately 3500 people suffer from cardiac arrest (CA) each year. CA and the resulting loss of blood flow to the brain often result in severe neurologic impairment. The aim of this study is to analyze the prognostic performance of NT-proBNP, NT-proANP, Copeptin, S-100B and neuron-specific enolase (NSE) within 24 h after CA.
- Methods: This study is a substudy in a multicenter randomized clinical trial and will be conducted from February 2013 until March 2015 at one medical institution in Denmark and one in Norway. Primary outcome is the comparison of the total biomarker release in the two groups. Secondary outcome is Glasgow-Pittsburgh Cerebral Performance Categories (CPC) score after 6 months dichotomized in good (CPC 1-2) and bad (CPC 3-5) outcome. We will use cut-off values, total release and change rate in serum of the biomarkers measured by AUC and compare with outcome. Goal is 100 consecutive comatose non-traumatic CA patients included. Blood is sampled on admission, at 24, 48 and 72 h after reaching target temperature of 33 degrees Celsius.
- Perspectives: Neurological damage is suggested to be accountable for 65% of mortality in patients treated with therapeutic hypothermia after out-of-hospital cardiac arrest. We hope to show that longer cooling diminishes the neural damage and thus the biomarker release and that a pooled panel of biomarkers will be able to predict 6 months outcome better than single biomarkers alone.
- P24.03      Sven Robert Andresen      THE EFFECT OF NORMAST (PEA) IN NEUROPATHIC PAIN IN SPINAL CORD INJURY  
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- Introduction/background: Neuropathic pain and spasticity after spinal cord injury represent significant but still unresolved problems, which cause considerable suffering and reduced quality of life for patients with spinal cord injury. Treatment is complicated and patients often receive

incomplete relief from present available and recommended treatment. Palmitoylethanolamide (PEA) is a fatty acid that is produced in many cells in the body, and it is thought to potentiate the body's own cannabis-like substances (endocannabinoids), and may reduce pain and inflammation. Clinical trials support the use of PEA on neuropathic pain and spasticity, but no studies are published in patients with spinal cord injury. Normast is a medical supplement which contains (PEA), and it is approved for use in Denmark.

**Aims:** To investigate the effect of Normast (PEA) on neuropathic pain and secondary on spasticity and psychological functioning in patients with spinal cord injury.

**Design and methods:** A randomized, double-blind, placebo-controlled parallel multicenter study. We will include 66 patients with neuropathic pain due to spinal cord injury. Multiple questionnaires regarding neuropathic pain, spasticity, insomnia, anxiety and depression are completed before and after treatment with either placebo or Normast. A numeric rating scale for pain intensity (0-10 point) is used to measure primary outcome.

**Present status and results:** Presently, 56 patients are included of which 49 have completed the trial. Recruitment is ongoing. No major side effects have been reported.

P24.04      Andreas      LARGE ANIMAL PARKINSONS DISEASE MODELS USING VIRAL VECTORS  
Nørgaard Glud      AND INOCULATION OF PREFORMED FIBRILS TO MEDIATE ALPHA-  
SYNUCLEIN OVEREXPRESSION AND MISFOLDING IN THE GÖTTINGEN  
MINIPIG CNS

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**Background:** Animal models towards understanding and treating Parkinson's disease (PD) are important translational steps toward clinical applications.

The Göttingen minipig (GM) fits progressional neurological models due to a relative low adult weight between 20-40 kg and has a large gyrencephalic brain (6x 5 x 4 cm) that can be examined at sufficient resolution using both conventional clinical scanning modalities and preclinical testing of deep brain stimulation, stem cell grafting and other neuromodulatory devices.

**Aim:** Using inoculating of human or pig alpha-synuclein (αSYN) fibrils or overexpressing αSYN using Lenti virus(LV) and Adeno Associated Virus(AAV) vectors in the nigrostriatal system, we hope to create a new

porcine model for PD.

Methods: Using conventional human-intended stereotaxic neurosurgery methods, we apply aSYN in the catecholamine nigrostriatal system of 13 GM.

The changes are quantified by neurological tests (behavior, scoring and gait), conventional and preclinical PET scanning modalities, autoradiography and post mortem histological evaluation.

Results: Studies are still ongoing and data is being collected. First results from LV methods showed "proof of concept" on gait and histology. Evaluation of gait, PET, autoradiography and histology are ongoing on AAV-models and awaiting on inoculation fibril-models.

Discussion: We predict that these animal models will be useful and beneficial in the understanding of pathological mechanisms of human PD, novel therapeutic strategies such as antiaggregant treatment, induced pluripotent stem cells or immunotherapy and development of novel radioligands for early diagnosis and assess disease progression.

P24.05      Rebeka Bodak      AUDITORY EXPOSURE AND THE ENHANCEMENT OF NEW MOTOR MEMORIES

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Brain imaging studies with highly skilled musicians show strong co-activation in the auditory and motor cortices during music performance. Interestingly, this co-activation has been shown while playing a familiar piece with no sound feedback, as well as during music listening in the absence of movement (Bangert et al., 2006; Lotze et al., 2003). After a short period of audio-motor training, this relationship between movement and sound production, known as audio-motor coupling, has also been observed in nonmusicians (Bangert & Altenmüller, 2003; Lahav et al., 2007).

Building on a recent behavioural study with nonmusicians by Stephan and colleagues (2014), this project will explore the impact of auditory exposure on the enhancement of new motor memories. Following an audiomotor mapping session, participants will be asked to listen to and memorise either Sequence A (Group A) or Sequence B (Group B). Using visuospatial stimuli to cue motor responses, all participants' will be tested using Sequence A before the mapping session, half of each group immediately after exposure, and the other half 30 days later. It is predicted that Congruent Group A will perform faster after exposure compared to before (within subjects), and that Congruent Group A will perform faster than Incongruent Group B (between subjects).

The findings of this study have the potential to be useful in motor rehabilitation settings where the coupling of sound and movement

patterns might help patients relearn motor tasks relevant to activities of daily living, particularly when regular physical practice is not possible.

P24.06 Krystian Figlewski

# TRANSCRANIAL DIRECT CURRENT STIMULATION COMBINED WITH TREADMILL TRAINING IN THE SUBACUTE PHASE FOLLOWING STROKE: CASE SERIES

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Background: Regaining walking ability after stroke is a major target in stroke rehabilitation. Imbalance of interhemispheric interactions is believed to interfere with the recovery process. This imbalance can be ameliorated by upregulation of the excitability in the lesioned hemisphere using non-invasive brain stimulation technique - transcranial Direct Current Stimulation (tDCS)

Aim: To evaluate the feasibility of anodal tDCS over lower limb primary motor cortex combined with body weight support treadmill training (BWSTT) in the subacute stroke patients.

Methods: 6 ischemic stroke patients included within 14 days from onset

Intervention:

1. BWSTT thrice per week for 4 weeks

2. Anodal tDCS:

- to the cortical lower limb motor area in affected hemisphere•2 mA current for 20 minutes during BWSTT using 35 cm<sup>2</sup> saline soaked electrodes

Evaluations:

- 10-meter walking test (10 MWT)

- isokinetic muscle strength of knee extensors using BIODEX System 3 Pro Dynamometer

- gait analysis (step length, swing time and stance time ratio) conducted with Vicon 612 8-camera system

Results: All subjects demonstrated improved gait velocity determined by the 10MWT. Gait analysis performed in 3 subjects revealed better temporal and spatial symmetry. No major side effects were reported.

Conclusion: Anodal tDCS combined with body weight support treadmill training is feasible and carries potential as a strategy to improve gait recovery in the early phase of stroke rehabilitation. Data represents preliminary results of an ongoing study which will include additional subjects in order to establish factors correlated with favorable outcome.

P24.07	Maryam Anzabi	<p>INFLUENCE OF PERICAPILLARY NITRIC OXIDE LEVELS AND EDEMA ON CAPILLARY BLOOD FLOW PATTERNS IN MOUSE MODELS OF SUBARACHNOID HEMORRHAGE</p> <p><i>M. Anzabi</i></p> <p>Center of Functionally Integrative Neuroscience (CFIN), Aarhus university</p> <p>Introduction: Subarachnoid hemorrhage (SAH) is a devastating disease associated with death and poor functional outcome. Despite decades of intense research and improvements in clinical management, delayed cerebral ischemia (DCI) remains the most important cause of morbidity and mortality after SAH. The key role of angiographic cerebral vasospasm, thought to be the main cause of DCI, has been questioned recently and over the last years, cerebrovasculature widespread constriction has been identified as a potential mechanism contributing to DCI. Nitrite administration has been shown to prevent vasospasm and can increase tissue survival. Hypertonic saline (HS) would also be expected to reduce edema and improve outcome.</p> <p>Aims: To assess the effect of pericapillary nitric oxide levels restoration by nitrite administration and edema reduction by (HS) on capillary flow patterns in SAH mouse model and further to serve as novel therapeutic targets.</p> <p>Materials and methods:</p> <p>SAH induction: A filament is advanced to skull base via internal carotid artery. At the branching point of middle cerebral artery the filament perforates the vessel and induces bleeding.</p> <p>Treatment studies:</p> <p>Treatment study 1: Sodium nitrite administration</p> <p>Treatment study 2: Hypertonic saline administration</p> <p>Capillary flow pattern evaluation:</p> <p>Optical coherence tomography built into two-photon microscopy will be recruited.</p> <p>Cerebral edema assessment:</p> <p>Diffusion weighted magnetic resonance imaging will be used during typical time period for edema formation.</p> <p>Perspectives: The project may provide new insights leading to better understanding of capillary flow pattern changes and predict treatment response during SAH and the following recovery period.</p>
P24.08	Trine Gjerløff	<p>THE NOVEL PET TRACER <sup>11</sup>C-DONEPEZIL DEMONSTRATES DECREASED PARASYMPATHETIC INNERVATION IN THE GUT AND PANCREAS OF PATIENTS WITH PARKINSON'S DISEASE</p> <p><i>T. Gjerløff<sup>1,2</sup>, T. Fedorova<sup>2</sup>, K. Knudsen<sup>2</sup>, O.L. Munk<sup>2</sup>, A. Nahimi<sup>1,2</sup>,</i></p>



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Parkinson's disease (PD) is characterized by early parasympathetic dysfunction leading to constipation and gastroparesis, but our understanding of the pathogenesis is limited. It was recently suggested that  $\alpha$ -synuclein aggregations originate in the gut and ascend to the brainstem via the vagus.

Donepezil is a high-affinity ligand for acetylcholinesterase - the breakdown enzyme in cholinergic synapses. Our aim was to validate [<sup>11</sup>C]-donepezil positron emission tomography (PET) as an imaging tool for visualizing parasympathetic denervation in PD.

We studied 12 patients with early-to-moderate PD (3 female; age 64±9 years) and 12 matched control subjects (3 female; age 62±8 years). We collected clinical information about motor severity, constipation, and gastroparesis. Heart rate variability measurements and gastric emptying scintigraphies were performed to obtain objective measures of parasympathetic symptoms.

Significantly decreased [<sup>11</sup>C]donepezil binding was detected in the small intestine (-35%; p=0.003) and pancreas (-22%; p=0.001) of the patients. No correlations were found between the [<sup>11</sup>C]donepezil signal and disease duration, constipation, gastric emptying time, and heart rate variability.

In PD, the dorsal motor nucleus of the vagus undergoes severe degeneration, and pathological  $\alpha$ -synuclein aggregations are present in the gastrointestinal tract. The majority of these aggregations are found in nerve fibres, including vagal efferents. In contrast, the enteric nervous system displays little or no loss of cholinergic neurons. The decrease in [<sup>11</sup>C]donepezil binding may therefore be the first successful marker of parasympathetic denervation of internal organs.

P24.09      Omar Majed      THE SOLUBLE RECEPTOR FOR VITAMIN B12 UPTAKE (SCD320) IS PRESENT  
Abuyaman      IN CEREBROSPINAL FLUID AND CORRELATES TO THE DEMENTIA MARKERS  
TAU PROTEINS AND AMYLOID BETA

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Background: Cellular uptake of vitamin B12 (B12) demands binding of the vitamin to transcobalamin (TC) and recognition of TC-B12 (holoTC) by the receptor CD320. Recently, we identified a soluble form of CD320 (sCD320) in human plasma. Here we present data on the occurrence of this soluble receptor in cerebrospinal fluid (CSF) and reveal its correlations to

biomarkers of dementia; tau proteins and amyloid-beta.

Methods: We collected 223 cerebrospinal fluid samples and corresponding plasma samples to 46 of those. We measured CSF and plasma sCD320, holoTC and total TC employing in-house ELISA methods and CSF phospho-tau (181P), tau and amyloid-beta (1-42) employing commercial ELISA kits (Innogenetics Company).

Results: The median sCD320 concentration in CSF (14 pmol/L) is around five times lower than in plasma (72 pmol/L). No correlation was observed between plasma and CSF levels. In CSF, sCD320 correlate to holoTC and total TC (Spearman's correlation ( $R_s$ ) = 0.325, 0.232 respectively,  $P < 0.01$ ). Interestingly, sCD320 correlate to phospho-tau and tau ( $R_s = 0.599$ ,  $0.569$  respectively,  $P < 0.001$ ) and to amyloid-beta ( $R_s = 0.265$ ,  $P < 0.001$ ). Patients biochemically classified as Alzheimer's dementia because of high tau proteins and low amyloid beta ( $n = 18$ ) showed significantly higher values of sCD320 in CSF (median 17 pmol/L) than the remaining group ( $n = 159$ , median 13 pmol/L).

Conclusion: We document for the first time the occurrence of sCD320 in human CSF. We report that the concentration of sCD320 correlate to the dementia biomarkers, phospho-tau, tau and amyloid-beta. Further studies are requested to explore the potential of sCD320 as a biomarker for dementia and neuronal degeneration.

P24.10      Lena-Sophie      COGNITIVE PHENOTYPING OF A RAT CMS DEPRESSION MODEL USING  
Martis                      TOUCHSCREEN OPERANT PLATFORM

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Major depressive disorder (MDD) is one of the leading causes for disability worldwide with a growing number of cases. MDD displays a burden for both the affected individuals as well as the society. The development and verification of antidepressant treatment strategies are vital to optimize therapy for patients and, hence, well established and validated MDD animal models are crucial. In humans, stress was shown to be the main environmental risk factor for developing depression emphasizing the use of a rodent chronic mild stress (CMS) model in MDD research. Rodents exposed to CMS reveal a diminished interest in activities which were perceived rewarding prior to stress onset giving rise to a core symptom of MDD, termed anhedonia. Further key symptoms of MDD are cognitive decline, bias for negative information and memory problems. Tests, such as Morris water and elevated plus maze, are selected to evaluate these symptoms albeit the translational value to the clinic is poor. Therefore, we plan to evaluate the validity of our CMS model in regard to cognition with the touchscreen (TS) operant platform. This method is thought to enable adequate translational testing between animals and humans. A battery of TS tests, such as paired-associate learning, is available allowing the screening of cognition, attention and memory all in the same animal. Moreover, the application of the TS is simple, its automation reduces examiner effects to a minimum and it provides an objective readout of the animals' response along with its cognitive abilities. The translational TS

technique offers a great perspective for advanced testing of pro-cognitive drug treatment in animal models.

- P25.01      Brigitta Villumsen      THE IMPACT OF EXERCISE IN MEN WITH PROSTATE CANCER RECEIVING ANDROGEN DEPRIVATION THERAPY
- B.R. Villumsen<sup>1</sup>, B. Hørdam<sup>2</sup>, M.G. Jørgensen<sup>3</sup>, J. Frystyk<sup>1</sup>, M. Borre<sup>1</sup>*
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- Introduction: Decreased quality of life, fatigue, type 2 diabetes and cardiovascular diseases are well known side effects to androgen deprivation therapy in prostate cancer patients. These conditions can be prevented and treated with exercise. However, studies on home-based exercise are called for because patients prefer to exercise at home or with family members.
- Objective: To determine the efficacy of a 12-week home-based exercise program on physical function, body composition, quality of life, fatigue and metabolic parameters.
- Methods: The study will be performed as a randomised study.
- Two groups: a) intervention group (n=23) and b) control group (n=23). Intervention: home-based exercise 60 minutes 3 times per week for 12 weeks using the Xbox Kinect and free weights. Physical tests: 6 minute walk test, leg extensor power, bioelectrical impedance analysis.
- Questionnaires: EORTC QLQ-C 30, Functional Assessment of Cancer Therapy-Prostate (FACT-P), Functional assessment of chronic illness therapy - Fatigue (FACIT-F).
- Blood samples: Insulin sensitivity, adiponectin, Insulin-like Growth Factor-1 (IGF-1) and Insulin-like Growth Factor Binding Proteins (IGF-BP), blood pressure, body mass index (BMI), waist circumference.
- Inclusion criteria: Men with prostate cancer receiving androgen deprivation therapy for > 3 months, performance status 0-1.
- Exclusion criteria: Men with castration resistant prostate cancer, intense cardio exercise or strength training > 2 times per week within 3 months prior to inclusion.
- Conclusion: This project is expected to provide knowledge about a novel exercise modality for prostate cancer patients giving them the possibility to overcome treatment related side effects.
- P25.02      Lise Høj Thomsen      IDENTIFICATION OF TGF- $\beta$  DEPENDENT/INDEPENDENT PATHWAYS IN ANIMAL MODELS OF EARLY-STAGE DIABETIC NEPHROPATHY

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**Purpose:** Diabetic Nephropathy (DN) is the main cause of end-stage-renal-disease in the western world. DN is characterised by the development of fibrosis where the TGF- $\beta$  superfamily is regulated. Due to the poor translation from animal models into the human late stage complications, this study aims to identify early-stage changes within the TGF- $\beta$  superfamily in the animal models.

**Methods:** SV129 mice were induced with diabetes using streptozotocin (double intermediate dose; 125mg/kg) or vehicle (controls). Db/db mice were also used. After 13 weeks of hyperglycemia, animals were sacrificed; kidneys were isolated and embedded in paraffin. These were stained for H&E, PAS, Sirius red and pSmad1/5/8 and pSmad2. Another group of STZ and db/db was used for gene expression. Present were two different time points of 10 and 18 weeks of STZ mice. The db/db animals were sacrificed after 15 weeks of hyperglycemia and the kidneys isolated. Differences in gene expression of selected targets of the TGF- $\beta$  superfamily were analysed using TaqMan Array Cards containing 44 selected markers, including TGF- $\beta$  and BMP end-genes, BMP modulators, ligands and EMT markers.

**Results and conclusions:** We found an increase in the early-stage STZ model of the nuclear expression of pSmad2 in distal tubuli which correlates with dilated lumen of distal tubuli and gene upregulation of PAI-1. An increase in gene expression of TGF- $\beta$ 2 and activin A was found, and these ligands follow this pathway. Targeting this pathway and its modulators early in disease might be a potential alternative in the prevention of DN.

P25.03      Hanne Mari Jørgensen      N-3 POLYUNSATURATED FATTY ACIDS AND BONE DENSITY IN RENAL TRANSPLANT RECIPIENTS

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**Background:** n-3 polyunsaturated fatty acids (n-3 PUFA) may have beneficial effects on bone. Renal transplant recipients (RTR) suffer high fracture rates, significantly affecting long-term outcome after renal transplantation. The aim of this study was to investigate the association between plasma n-3 PUFA and bone mineral density (BMD) in a large cohort of Norwegian RTR.

Material and methods: A total of 701 patients who received a renal transplant at Oslo University Hospital were included. BMD measurements and blood samples were done 10 weeks post-transplant. Multiple linear regression was used to assess the association between n-3 PUFA and BMD.

Results: Patients were on average 53.9 (range 41.5,64.0) years of age, and two thirds were men. Preemptive renal transplantation was performed in 28%, 149 had received peritoneal dialysis and 399 hemodialysis. Diabetic nephropathy was present in 15%. Median n-3 PUFA was 7.75% (range 5.94, 9.84). By femoral neck T-score, a quarter of patients were osteoporotic (n=176), and an additional half were osteopenic (n=353). There were positive associations between n-3 PUFA and BMD at total hip ( $\beta=0.0041$ ,  $p=0.017$ ) and lumbar spine ( $\beta=0.0058$ ,  $p=0.022$ ) after multivariate adjustment. Positive, but not significant, associations were found between n-3 PUFA and BMD at femoral neck, total body, proximal third and ultradistal radius.

Conclusion: This study is the first to investigate the relationship between n-3 PUFA and BMD in a large cohort of RTR. We found a positive association between n-3 PUFA and BMD at the hip and lumbar spine. More studies are warranted to investigate possible beneficial effects of n-3 PUFA on bone in RTR.

- P25.04      Pernille Skjold Kingo      C-REACTIVE PROTEIN CONCENTRATION - COMPARISON BETWEEN ROBOT-ASSISTED LAPAROSCOPIC CYSTECTOMY AND OPEN MINI-LAPAROTOMY CYSTECTOMY

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Introduction and objective: Cystectomy, like other traumas to the body, induces a stress response (SR) which plays an important role in controlling the human immune system. A widely used parameter for SR is serum levels of C-reactive protein (CRP). This study aims to compare the different surgical cystectomy procedures in relation to CRP concentration.

Methods and materials: 109 patients (83 men) with MIBC underwent a radical cystectomy with an ileal conduit. Either open mini-laparotomy cx (OC) (n=86), Robot-ass. laparoscopic cx with extracorporeal urinary diversion (RALC-ex, n=14), or Robot-ass. laparoscopic cx with intracorporeal urinary diversion (RALC-in, n=9) was performed. Blood samples were obtained preoperative and postoperative (day 1-4). ASA-score, BMI, comorbidities (Charlson score), clinical stage, blood loss, operating room time (OR), admission time, pre- and post-operative complications (Clavien score) were recorded.

Results: No differences between OP types were found in age, gender, BMI, ASA, or clinical stage. Charlson scores were higher in the OC than the RALC-in group. Blood loss was higher in the OC group and OR was longer in the RALC groups, while no difference was found comparing the two RALC groups. There were no differences in preoperative CRP, overall

Clavien score and hospital stay. CRP peaked on postoperative day 3 in the RALC-in group and on day 2 in the OC and RALC-ex groups who also had a generally lower CRP concentration than the RALC-in group.

Conclusion: This study indicates that the RALC-in is associated with a higher level of postoperative CRP than the OC and RALC-ex procedures. Ongoing studies investigate the reasons for these differences.

P25.05 Tommy  
Kjærgaard  
Nielsen

#### LAPAROSCOPIC CRYOABLATION OF SMALL RENAL TUMORS - DOES ANATOMICAL TUMOR COMPLEXITY EFFECT TREATMENT OUTCOME?

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Aim: The aim of the present study was to investigate whether patients with an anatomical complex tumor, represented by a high PADUA-score ( $\geq 10$ ), carried a higher risk of residual unablated tumor compared to patients with a less anatomical complex tumor when treated with laparoscopic cryoablation.

Material and methods: A retrospective review of Aarhus Cryoablation Register identified 120 patients with a single biopsy-verified pT1a renal tumor, treated with primary laparoscopic cryoablation between August 2005 and December 2013.

Results: Mean patient age: 63 years (95%CI 61;65). Mean BMI: 27 kg/m<sup>2</sup> (95%CI 26;28). Mean ASA-score: 2.1 (95%CI 2;2.2). Mean tumor size: 27 mm (95%CI 26;29). Mean follow-up time: 24 months (95%CI 20;27). PADUA-score was found to be low or moderate ( $< 10$ ) in 93 patients (77.5%) and high ( $\geq 10$ ) in 24 patients (20%). In 3 patients (2.5%) the PADUA-score could not be obtained. Residual unablated tumor was diagnosed in 8/93 patients (8.6%) with a low-moderate PADUA-scoring tumor compared to 6/24 patients (25%) with a high PADUA-scoring tumor. This relative risk of 2.9 (95%CI 1.1;7.6) was statistically significant ( $p=0.03$ ). The mean follow-up time from treatment to diagnosis of treatment failure was 13 months (95%CI 8;18), which was not found to be significantly different between the two groups.

Conclusion: Patients with an anatomical complex tumor, represented by a PADUA-score  $\geq 10$  carries a significantly higher risk of residual unablated tumor compared to patients with a less anatomical complex tumor, when treated with laparoscopic cryoablation.

P25.06 Steven  
Brantlov

#### BIOIMPEDANCE ANALYSIS IN CHILDREN AGED 0-14 YEARS: IS THERE A RELATION BETWEEN PHASE ANGLE, WEIGHT AND BODY SURFACE AREA?

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Background and aim: Knowledge of fluid compartment changes and nutritional status is crucial when evaluating critically ill children, as well as measuring the effect of treatment. Current reference methods (DXA, dilution-methods etc.) are invasive, expensive, and/or time consuming and are therefore not suitable for routine paediatric examination.

Bioimpedance analysis (BIA) offers an alternative to this since it is non-invasive, simple, portable and inexpensive. One BIA approach is to use values of total body fluid (TBF), extra- and intra-cellular fluid (ECF, ICF) and/or body cell mass (BCM). These are based on predictive equations and proven only in adults. Another approach is to use the phase angle (PA), which is a combination between the electrical resistance (R) of the electrolytic-containing TBF and the capacitive reactance ( $X_C$ ) of the cell membrane, both expressed in ohms ( $\Omega$ ). PA is an indicator of fluid compartment changes and cell membrane properties.

Aim: To investigate the relation between PA and weight (kg) and the body surface area, BSA ( $m^2$ ).

Methods: Whole-body BIA was performed in 47 healthy children (boys=33, girls=14, 0-14 yr). PA ( $\arctan = X_C/R$ , degrees) was measured at 50-kHz with a bioimpedance spectroscopy device (Xitron 4200). Statistics: Spearman's rank correlation (r),  $P < 0.05$  and a 95% confidence interval.

Results: Data showed high positive correlations between PA and weight (0.74,  $P < 0.0001$ ) and BSA (0.75,  $P < 0.0001$ ).

Conclusions: PA offers promising perspectives for further research areas (e.g. gender influence on PA). Potentially, PA could be a new way of monitoring fluid compartment changes and nutritional status in critically ill children.

P25.07      Maria Elkjær      MULTI-PARAMETRIC MAGNETIC RESONANCE IMAGING IN THE DIAGNOSIS AND SURVEILLANCE OF PROSTATE CANCER

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Background: Patients with 'low risk' prostate cancer (PC) often undergo active surveillance (AS), rather than active surgical treatment (RP). However, PC tumor load and aggressiveness are typically underestimated. Multi-parametric magnetic resonance imaging (mMRI) and MRI guided biopsies (MRGB) have undergone significant technical improvements and have continuously been optimized for detection of PC.

Aims: To investigate the hypothesis that 1) mMRI and MRGB provide a more accurate and secure interpretation of the aggressiveness of PC initially defined as low risk and that 2) mMRI can be used to map PC tumors, both in terms of aggressiveness and tumor load, in a thorough and precise matter.

Patients and methods: We will conduct three studies: 1) A retrospective,

descriptive study of AS and RP patients referred to the department in 2009-2011. We will describe the population in terms of patient demographics, cancer risk classification, tumor load, treatment strategy and progression. 2) A prospective study of 60 patients, put in AS, who will have an additional mMRI scan. If suspicious of significant cancer, MRGB will be taken. 3) A descriptive study of 200 patients planned to be radically prostatectomized. They will have a pre-surgery mMRI scan. Blinded to the histology the scans will be assessed and afterwards compared to the pathological results.

Results: For study 1, first results are expected in early 2015. For studies 2 and 3, enrolment has just started, and we expect to have the first results late in 2015.

P25.08      Danny Jensen      THE ESSENTIAL ROLE OF PROXIMAL TUBULE ENDOCYTIC RECEPTORS FOR THE URINARY EXCRETION OF ENDOGENOUS CYSTATIN C

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Background: Urinary cystatin C is an established marker of kidney injury. Cystatin C is freely filtered in the glomeruli and normally completely reabsorbed by the proximal tubules. Megalin and cubilin are proximal tubule endocytic receptors important for reabsorption of filtered proteins. This study examines the role of these receptors for the tubular uptake and urinary excretion of endogenous cystatin C.

Methods: Binding of recombinant cystatin C to purified megalin and cubilin was analyzed by surface plasmon resonance analysis. Urinary excretion and proximal tubular uptake of endogenous cystatin C was studied by immunoblotting and immunohistochemistry in wildtype and in conditional cubilin/ megalin double KO mice ( $cub^{-/-}/meg^{-/-}$ ) and cubilin KO mice ( $cub^{-/-}$ ).

Results: A high affinity binding of cystatin C to megalin ( $K_d \sim 32$  nM) and to cubilin ( $K_d \sim 24$  nM) was identified. Receptor Associated Protein (RAP), an established high affinity ligand to megalin, completely abolished cystatin C binding to megalin. In  $cub^{-/-}/meg^{-/-}$  mice, increased urinary excretion of cystatin C was observed along with reduced proximal tubule endocytosis. Normal proximal tubule uptake and no urinary excretion of cystatin C were identified in  $cub^{-/-}$  and wildtype mice.

Conclusions: The endocytic receptors megalin and cubilin bind cystatin C with high affinity, but only megalin is essential for the normal tubular recovery of endogenous cystatin C. Thus, increased urinary excretion of cystatin C is a marker of megalin dysfunction.

P25.09      Casper Kierulf Lassen      THE ROLE OF REMOTE ISCHEMIC CONDITIONING IN RENAL ISCHEMIA-REPERFUSION INJURY

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**Background:** Ischemia-reperfusion injury is the leading cause of acute kidney injury. Brief episodes of intermittent ischemia and reperfusion applied to a distant organ termed remote ischemic conditioning (rIC) can protect the kidney against this injury. In this study, we investigated the effect of 4 times 5 min/5 min ischemia and reperfusion by clamping the infrarenal aorta during 37 min of warm renal ischemia in a unilateral nephrectomized rat model.

**Method:** One week after right-sided nephrectomy Wistar rats were randomly divided into 3 groups; sham I/R (n=7), I/R (n=10) and I/R+rIC (n=10) and underwent either sham operation or 37 min of warm renal ischemia. Urine and blood were sampled 72 hours and 7 days after reperfusion to determine kidney function. The kidney was harvested to evaluate markers of kidney injury, oxidative stress and apoptosis.

**Results:** Seventy-two hours after reperfusion, the ischemic groups demonstrated a significantly reduced kidney function compared to the sham group as evidenced by creatinine clearance with no significant effect of rIC (I/R+rIC; 1.68 [1.07;2.28] ml/min/kg vs. I/R; 1.72 [0.90;2.55] ml/min/kg, p>0.05). Compared to the I/R group, rIC reduced the expression of kidney injury marker NGAL by 50% (p=0.033).

**Conclusion:** In our study, remote ischemic conditioning did not protect the kidney against ischemia-reperfusion injury in terms of kidney function. However, rIC significantly reduced the kidney injury marker NGAL.

P25.10      Michael Christensen      RENOPROTECTIVE EFFECTS OF METFORMIN IN RESPONSE TO UNILATERAL URETERAL OBSTRUCTION IN MICE

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Metformin is the first choice treatment for type-2 diabetes where it among others has glucose stabilizing effects. In this study, we examined the effect of metformin on the progression of tubular injury, inflammation and oxidative stress in response to unilateral ureteral obstruction (UUO). C57bl/6 mice were treated with metformin (500mg/kg/day) 7 days prior to obstruction, as well as 3 days post obstruction. Hematoxylin and eosin staining showed lesser tubular dilation in the metformin treated UUO group (UUO-MET) compared to UUO. Kidney injury molecule-1 a specific marker for proximal tubule damage was markedly increased in the obstructed kidney of UUO mice, and this increase was partly normalized in the UUO-MET. UUO increased inflammatory markers TNF $\alpha$  and interleukin-6, which was attenuated in response to metformin administration. The M1 macrophage marker integrin  $\alpha$ X was expressed to a lesser extent in the metformin treated UUO mice, indicating lesser macrophage infiltration. Besides a downregulation of inflammatory markers, there was an increase in the abundance of the antioxidants protein heme oxygenase-1 and

superoxide dismutase-1 in the UUO-MET mice compared to untreated UUO mice. Mice receiving metformin had elevated plasma levels of lactate both in SHAM and UUO groups, indicating that metformin was successfully administered to the mice. Plasma creatinine and urea were unchanged after metformin administration in response to UUO. In conclusion, this study indicates that metformin attenuates the progression of tubular injury, inflammation and oxidative stress in mice exposed to a 3-day UUO.

P26.01 Anne Wandler MICRORNA EXPRESSION DIFFERS BETWEEN MELANOCYTIC NEVI AND MELANOMA - A MICROARRAY ANALYSIS

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Introduction: Melanoma is a potentially lethal cancer with increasing incidence. MicroRNAs (miRNAs) are short non-coding RNAs involved in diverse cellular functions. miRNAs are deregulated in many types of cancer, including melanoma. To explore their role in melanoma, we used miRNA array analysis to investigate differences in miRNA expression between 20 benign dermal melanocytic nevi and 20 dermal melanomas (all formalin-fixed and paraffin-embedded).

Methods: Total RNA was purified from tumour core biopsies, and a dual-colour array analysis was conducted (Exiqon Services, Denmark), according to standard protocols. In brief, total RNA from all samples and a common reference pool were labelled with different fluorophores. The labelled samples and the reference RNA were mixed pair-wise and hybridized to the miRCURY LNA<sup>TM</sup> microRNA Array 7th Gen, containing capture probes targeting all miRNAs registered in the miRBase 18.0. Slides were then scanned and image analysis was carried out. The quantified signals were background corrected and normalized prior to statistical analysis.

Results: With an absolute log fold change larger than 1, an adjusted p-value below 0.05, with standard signal intensities, the profiling analysis identified 77 differentially expressed miRNAs, e.g. miR-21-5p and miR-125b-5p.

Conclusion: Our study shows that miRNA expression differs between melanocytic nevi and melanoma. We will further validate these results by qPCR and in situ hybridisation in new tissue cohorts, in order to begin to establish their possible biological significance.

P26.02 Chaitali Laura Ollars BEREAVEMENT SUPPORT IN PALLIATIVE CARE - A RANDOMISED CONTROLLED TRIAL (RCT)

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Background: According to WHO, bereavement support is an important part of palliative care. 10-15% of bereaved relatives experience grief reaction of a persistent and debilitating nature, also referred to as Complicated Grief (CG). Studies associate CG with co-morbidity, increased use of medicine and increased mortality. In Denmark, there are no standards for bereavement support and there is a lack of empirically tested support strategies.

Aim: The aim of this study is to test if a systematic bereavement support strategy in specialised palliative care units in Denmark will increase identification of support needs, psychological wellbeing and CG, and if it will optimise utilisation of healthcare resources.

Method: The study is designed as an RCT. Specialised palliative care teams in the Central Region Denmark are divided into intervention or usual care teams. 300 relatives will be cluster randomised to each group. The intervention is administered by the palliative team: 1) At referral, the team performs a CG risk assessment; 2) If support is needed, a case record is created; 3) When contact to the relative is ended, a note is sent to the general practitioner. Data is collected via three questionnaires: At baseline and two follow-up questionnaires at 1 and 6 months after death.

Perspectives: Systematic bereavement support may help early identification of support needs and CG and may also facilitate targeted treatment. Empirically tested bereavement support strategies could help develop clinically relevant support standards and optimise specialised palliative care in Denmark in accordance to international standards.

P26.03      Marianne      ADVANCE CARE PLANNING IN DENMARK

Hjorth

Skorstengaard

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Background: Advance Care Planning (ACP) is a way to improve the quality of end-of-life care. ACP is a discussion between an incurably ill patient, a health care professional and, if possible, a relative about preferences for end-of-life care.

Aim: To investigate if ACP is effective in relation to improving incurably ill patients' quality of life, satisfaction with health care services, and to reduce the psychological distress among both patients and bereaved relatives.

Methods: The study is a randomised controlled trial. Eligible patients from departments of oncology, cardiology, and respiratory medicine at AUH are

included and randomised into two groups: one receiving usual care and one receiving usual care and ACP. ACP discussions will be documented in the Electronic Patient Files and sent to the general practitioner and community nurse with the patient's acceptance. Patients and relatives will be followed with questionnaires to monitor quality of life, satisfaction with provided care, anxiety and psychological distress. Patients' preferences regarding place of care and death will be registered. 65 patients from each department will be included in the study. Inclusion began November 2013 and ends July 2015. Until now, a total of 95 patients has been included (37 cancer patients, 40 lung patients, and 18 heart patients).

Perspectives: If ACP is found effective, it has potential to improve quality of end-of-life care for patients and their families, to reduce uncertainty experienced by many patients and their relatives with substantial psychological distress as consequence, and finally to make discussions concerning resuscitation easier for both patient and professional.

P26.04 Kennet S nderstgaard Thorup INTRAVOXEL INCOHERENT MOTION (IVIM) ANALYSIS OF DIFFUSION WEIGHTED MAGNETIC RESONANCE IMAGING (DWI) ALLOWS ESTIMATION OF DIFFUSION AND PERFUSION DIFFUSION RELATED PARAMETERS

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Background: When using IVIM in tumor characterization, the minimum requirements for image quality to ensure an acceptable accuracy and reproducibility are unknown.

Aim: To determine the minimum requirements for image quality to ensure an acceptable accuracy and reproducibility to calculate IVIM parameters: diffusion coefficient (D), perfusion fraction (f) and pseudodiffusion (D\*).

Method: A computer model has been developed in MATLAB. Parameters the model can test include: signal to noise ratio (SNR), tumor size, tumor motion and image resolution. When changing the model parameters gradually, and looking at the root mean square error (RMSE) of the results, it is possible to see the resulting error in the IVIM calculations.

Initial results: Imaging matrix, SNR, tumor size and tumor movement all influence IVIM calculations, but the biggest error was introduced due to motion. Small tumors were generally more sensitive to parameter changes and required a higher quality scan to be correctly characterized. Even at a small motion (1 mm), the relative RMSE was over 100 % for a tumor with a diameter of 12 mm for D\*. D and f were more robust and stayed below a relative RMSE of 15% at 1mm motion. In large tumors (41mm), the IVIM calculations with a motion up to 3mm still revealed relative RMSE of 15 %.

Conclusion: SNR should be above 30 and motion should not exceed 2mm when characterizing tumors with IVIM. Imaging resolution has the least influence on IVIM parameters. Tumor sizes below 20mm induce increasing

errors and require a high degree of motion control.

Future perspective: In vivo studies guided by these results will be made to further validate the IVIM method.

P26.05      Kim Sivesgaard      WHOLE BODY MRI COULD AID IN THE DETECTION OF EXTRA-HEPATIC COLORECTAL CANCER METASTASES

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Background: Whole Body MRI has recently become feasible. It provides possibility for a comprehensive one-stop shop for detecting possible further dissemination in addition to an assumed superior evaluation of colorectal liver metastases. However, the most appropriate combination of MRI sequences for extra-hepatic metastases needs to be defined.

Aim: To assess the diagnostic accuracy of different MRI sequences for detection of extra-hepatic colorectal metastases and define the most appropriate combination of MRI sequences to be used in a future protocol combined with comprehensive MRI of the liver.

Method: 30 patients with extra-hepatic disseminated colorectal cancer will be scanned with 6 MRI sequences covering the neck to mid-thigh on a 1.5 T MRI scanner equipped for whole body scanning. For reference the patients will receive a PET/CT. An analysis of sensitivity for regional detection of metastases (lungs, lymph nodes, peritoneum, local recurrence, bone and other) will be made with PET/CT as reference. The minimum number of MRI sequences with sufficient accuracy for detecting extra-hepatic dissemination will be determined.

Results: So far 8 patients have been scanned and promising image quality has been observed. However, accurate analysis is pending more patients.

Perspective: A definition of the accurate and time-efficient combination of whole body MRI sequences will facilitate a future study of using MRI for screening of extra-hepatic metastases in patients planned for local treatment of colorectal liver metastases.

P26.06      Anne Kruse      ENHANCED MICRORNA SUPPRESSION ACTIVITY OF RNA POL II-  
Hollensen      TRANSCRIBED TOUGH DECOY INHIBITORS FUSED TO WPRE

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Dysregulation of microRNA (miRNA) expression, and thus changed expression of miRNA target genes, is associated with development of a range of diseases. To achieve efficient suppression of miRNA activity in experimental and therapeutic contexts, different miRNA inhibitor designs have been studied. Previously, we showed high potency of vector-encoded hairpin-shaped Tough Decoy (TuD) miRNA inhibitors and improved the design to obtain increased and synchronized inhibition of two or more miRNAs. To further refine the guidelines for production of efficacious RNA pol II-transcribed TuDs, we studied here the importance of the Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element (WPRE) for function of vector-encoded TuDs. For a panel of four TuDs, each targeting a specific miRNA, we consistently observed levels of suppression that were twofold higher when the TuD was fused to the WPRE RNA element relative to TuDs without WPRE. These findings indicate that optimized nucleocytoplasmic transport is crucial for TuD function and that the inclusion of WPRE is essential for miRNA suppression by RNA pol II-transcribed TuDs. Based on the discovery of naturally occurring circular RNAs with miRNA sponge activity, we hypothesized that TuD function could be further improved in the context of RNA circles. Notably, miR-7-targeting TuDs suppressed miR-7 activity with more than four-fold higher efficiency than an expressed circular RNA sponge containing 73 seed-targets for miR-7. We have initiated the production of circular RNAs containing TuDs targeting a panel of miRNAs and are currently investigating the potential anti-miR activity of such engineered miRNA suppressors.

P26.07      Ninna Cathrine REGULATION OF ACID-BASE BALANCE AND BLOOD PERFUSION IN  
Schmidt Voss      HUMAN COLON CANCER

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The metabolism of cancer tissue is high and partially glycolytic even under aerobic conditions. Despite accumulation of acidic waste products in the tumor microenvironment, intracellular pH of cancer cells is neutral to alkaline. The characteristically low extracellular pH and high intracellular pH of cancer tissue are thought to facilitate cancer development and progression.

Purportedly, the unusual acid distribution of cancer tissue is related to changes in acid-base transporter expression and function. Na<sup>+</sup>/HCO<sub>3</sub><sup>-</sup>-cotransporter NBCe1 and Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup>-exchanger DRA are candidate acid-base exchangers in colon cancer, but their functional importance remains unsettled.

The high metabolism of cancer tissue also necessitates a substantial blood supply. The function of tumor arteries and mechanisms of regulation have not been well investigated.

Aims and hypotheses: It is the aim of this project to further our understanding of colon carcinogenesis and investigate the following

hypotheses:

- Cellular acid extrusion mechanisms are enhanced and cellular base extrusion mechanisms reduced in colon carcinomas compared to normal colon mucosa. These changes in transmembrane acid-base transport allow colon carcinomas to maintain an alkaline intracellular pH.
- Changes in expression of NBCe1 and DRA during colon carcinogenesis are paralleled by changes in  $\text{Na}^+/\text{HCO}_3^-$ -cotransport and  $\text{Cl}^-/\text{HCO}_3^-$ -exchange activity and related to changes in microRNA expression.
- Tumor blood vessels differ functionally and structurally from corresponding normal blood vessels and, based on differences in agonist responses, tumor arteries can be targeted selectively to enhance or reduce tumor blood perfusion.

P26.08      Morten  
                 Nørgaard  
                 Andersen

LIPOSOME-BASED SPECIFIC TARGETING OF DRUGS TO CANCER-  
PROMOTING MACROPHAGES: A NOVEL THERAPUTIC PARADIGM IN  
MULTIPLE MYELOMA

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Background: Tumor-associated macrophages (TAMs) play an important role in cancer by suppression of adaptive immunity and promotion of angiogenesis and metastasis. Infiltration by TAMs is associated to poor prognosis in most human malignancies. Importantly, expression of the haemoglobin scavenger receptor CD163 is markedly increased on TAMs. Activity of the transcription factor STAT3 is increased in both stromal and malignant cells, and has been proposed as a target for novel anti-cancer therapy. Ablation of the STAT3 gene, specifically in cells of the haematopoietic system, has been shown to elicit a strong anti-tumor immune response in a mouse model of melanoma. Therefore, CD163-targeted inhibition of STAT3 within TAMs may be a novel treatment paradigm in malignant diseases.

Materials and methods: In vitro, monocyte-derived macrophages (MDMs) were targeted using a liposome-based system, in which the molecule/drug of interest is packaged within long-circulating liposomes (LCLs). LCLs containing either green fluorescent protein calcein (cal-LCL) or the STAT3-inhibitor corosolic acid (CA-LCL) were produced.

Preliminary results: Here we show that cal-LCL uptake was markedly higher in the MDMs with the highest CD163 expression. This is important since human TAMs are believed to be among the most CD163 expressing cells. We have been able to produce LCLs containing high concentration of CA. Using a sensitive assay for detection of (activated) P-(Y705)-STAT3 by flow cytometry, we are currently examining the ability of this CD163-targeted

drug to inhibit STAT3 activation in MDMs.

Perspectives: This may lead to the first in vivo experiments of targeted inhibition of STAT3 in TAMs.

- P27.01 Birgitte Sandfeld Paulsen ULTRA-MICRO SAMPLES CAN BE USED FOR MRNA ANALYSIS FOR LUNG CANCER RELEVANT BIOMARKERS

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Background: Understanding genetic alterations is essential when treating non-small cell lung cancer (NSCLC), but isolation of sufficient material for molecular testing remains challenging. New ultra-microsamples (uMS) have been proven sufficient for DNA and mRNA identification, and this could complement the use of transbronchial needle aspirations and fine needle aspirations in the diagnostics of NSCLC. We investigated if uMS from lung cancer patients can be used for quantitative mRNA analysis.

Methods: uMS were collected from patients where lung cancer is suspected. mRNA was isolated from primary tumors and lymph nodes, reverse transcribed into cDNA and quantified with quantitative PCR. MET, HGF, EGFR and AR expression was analyzed and tumor-cell fraction was estimated in each sample.

Results: Expression of MET, HGF, EGFR and AR was evaluated in 90 samples with and without cancer cells. Expression of MET and EGFR was negligible in samples without cancer cells, demonstrating that mRNA expression studies can be performed without accounting for normal-cell contribution. Adjusting for tumor-cell fraction makes it possible to obtain a quantitative result. In contrast, no difference in HGF and AR mRNA expression was observed. This emphasizes the use of a collection of lung biopsies without tumor cells to exclude mRNAs where the expression interferes with the tumor-cell expression.

Conclusion: We demonstrated that uMS contain high-quality mRNA, and quantitative studies can be performed when the tumor cell fraction is considered. It is essential that biopsies with normal cells are investigated to determine if they contribute significantly to the mRNA expression.

- P27.02 Kristian Løvvik Juul-Dam EARLY DETECTION OF RELAPSE OF ACUTE MYELOID LEUKEMIA IN CHILDREN

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**Introduction:** Pediatric acute myeloid leukemia (AML) is a heterogeneous disease with an overall survival of 70%. Relapse is the event that in most cases heralds ultimate treatment failure as only 30-40% of children with relapse are ultimately cured. Increasing levels of minimal residual disease (MRD) in peripheral blood (PB) might predict impending relapse in childhood AML. However, absence and instability of valid MRD-markers in a large proportion of patients limit early detection of disease recurrence and allow unrecognized regrowth of the malignant clone until overt clinical relapse. Detection of molecular relapse may provide improved treatment options.

**Methods:** In a large Nordic cohort of pediatric relapsed AML patients, we aim to compare cytogenetics, genetics and immunophenotype at diagnosis and relapse. Data will be extracted from the NOPHO database or obtained from local records. Additional molecular analysis will be performed on archived material. Furthermore, we aim to evaluate the kinetics of new and well-established MRD-markers in PB in childhood AML patients in clinical remission (CR). PB samples will be collected from all patients at monthly intervals during CR for 12 months. In case of relapse, samples will be analyzed by qPCR and next generation sequencing.

**Perspectives:** We hope our study provides novel insights into molecular biology and pathogenesis of relapsed pediatric AML. Identification of new MRD-markers facilitates inclusion of more patients into personalized monitoring regimes. Our study may demonstrate MRD monitoring as a reliable predictor of imminent relapse facilitating early intervention in molecularly relapsed childhood AML patients.

- P27.03      Trine Majken Gade Bonnesen      LIVER DISEASES IN ADULT LIFE AFTER CHILDHOOD CANCER IN SCANDINAVIA (ALICCS): A POPULATION-BASED COHORT STUDY
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**Introduction:** Significant improvements in the treatment of childhood cancer over the past decades have resulted in a growing population of long-term survivors. With this, a variety of adverse outcomes has become more apparent. The aim of this study was to identify the association between childhood cancer and liver outcomes evaluated as the risk of hospitalization with liver diseases.

**Methods:** Hospitalizations for liver diseases were evaluated in a cohort of one-year survivors diagnosed with cancer before the age of 20 identified from the cancer registries in the Nordic countries. For each survivor, we

randomly selected 5 population comparison individuals. We used population-based registries to obtain information on hospitalizations for liver diseases. Absolute excess risk (AER) and standardized hospitalization rate ratio (RR) were calculated.

Results: Survivors were at increased risk of being hospitalized for any liver disease (RR=2.9; 95% confidence interval 2.6-3.3). Even 20 years after diagnosis, the risk was still increased (RR=1.8; 1.5-2.1). Survivors were found to have an AER for liver disease of 60 per 100 000 person-years. The risk of viral hepatitis was 2.8 (95% CI 1.9-2.8), toxic liver disease 5.8 (95% CI 3.3-7.9), and for cirrhosis of the liver the risk was 3.0 (95% CI 1.5-5.8). Survivors of leukemia (RR=8.9; 7.3-10.9) and hepatic tumors (RR=54.3; 33.0-89.3) had the highest risk of hospitalizations for a liver disease.

Conclusions: Survivors of childhood cancer are at increased risk of liver disease, in particularly survivors of leukemia and hepatic tumors. These findings emphasize the importance of focused follow-up of childhood cancer survivors.

P27.04      Jakob  
Toftgaard      MOVING METAL ARTIFACT REDUCTION IN CONE- BEAM CT SCANS WITH  
IMPLANTED CYLINDRICAL GOLD MARKERS

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Purpose/objective: Implanted gold markers for image-guided radiotherapy (IGRT) lead to streaking artifacts in cone-beam CT (CBCT) scans. Here we propose and investigate a method for automatic moving metal artifact reduction (MMAR) in CBCT scans with cylindrical gold markers.

Materials and methods: The MMAR CBCT reconstruction method uses an automatic marker segmentation method to find the marker position in all projections. Removing the marker from the projections was performed with the segmented marker positions plus knowledge about the marker shape. The MMAR reconstruction was performed retrospectively using a half-fan CBCT scan for 29 consecutive stereotactic body radiation therapy patients with 2-3 gold markers implanted in the liver. The metal artifacts of the MMAR reconstructions were scored and compared with a standard MAR.

Result: The markers were found with the same auto-segmentation settings in 27 CBCT scans, while two scans needed slightly changed settings to find all markers automatically in step 1 of the MMAR method. MMAR resulted in 15 scans with no streaking artifacts, 11 scans with 1-4 streaks, and 3 scans with severe streaking artifacts. The corresponding numbers for MAR were 8 (no streaks), 1 (1-4 streaks), and 20 (severe streaking artifacts). The MMAR method was superior to MAR in scans with more than 8mm 3D marker motion and comparable to MAR for scans with less than 8 mm motion.

Conclusion: An automatic method for MMAR in CBCT scans was proposed and shown to effectively remove almost all streaking artifacts in a large set of clinical CBCT scans with implanted gold markers in the liver.

- P27.05      Mette Skovgaard Christensen      EXPOSURE TO STYRENE AND RISK OF CANCER: A LONG-TERM FOLLOW-UP STUDY OF WORKERS IN THE DANISH REINFORCED PLASTICS INDUSTRY
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- Background: Styrene is an economically important chemical used in the production of reinforced plastics among other things. In the past decades, studies of workers exposed to styrene have shown diverse results according to the risk of cancer. In 2002, IARC classified styrene as possibly carcinogenic to humans. In 2011, styrene was included in the 12<sup>th</sup> Report on Carcinogens. However, it is still widely discussed if this classification is correct.
- Aim: The aim of this study is to investigate whether exposure to styrene increases the risk of cancer among workers in the Danish reinforced plastics industry.
- Materials and methods: The cohort consists of approx. 80,000 workers in the Danish reinforced plastics industry, originating from 481 companies ever producing reinforced plastics in Denmark 1964-2007. The population is accumulating approx. 1 million person years.
- 15,107 living subjects were invited to participate in an individual survey about work and confounder information. 76 % responded.
- The exposure assessment is based on a matrix consisting of styrene measurements collected from the companies (1962-2007) and company information (process, product, calendar year). The matrix is going to classify each worker with an estimate of exposure probability and level of exposure.
- Outcome information is found in the registries (Danish Cancer Registry, National Pathology Registry, and National Patient Registry) along with confounder information (Statistics Denmark and self reported).
- Initially, the risk assessment will be based on standardized incidence rate ratios (SIRs) along with detailed internal risk assessment for subgroups of cancer.

- P27.06      Oscar Casares Magaz      SPATIAL DOSE RESPONSE RELATIONS FOR RECTAL MORBIDITY FOLLOWING HIGH-PRECISION RADIOTHERAPY

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Prostate cancer is the most frequent cancer among men and rapidly increasing incidence over the past two decades; 60% of all men diagnosed will, at some time point, be referred to RT. The radiation dose that can safely be prescribed to prostate tumours is limited by the tolerance of the surrounding normal tissues, primarily by the rectum. The dose delivered to the rectum has been associated with the risk of developing late normal tissue morbidity. In particular, rectal bleeding is one of the most important consequences following prostate RT. Consequently, this adverse effect has been investigated in RT outcome, where high doses have been found to be predictive for rectal bleeding. However, the effect of intermediate doses, spatial dose-response and how these relations are influenced by the considerable rectal motion patterns has so far received little attention.

The overall aim of the PhD project is to establish methods for assessing the spatial dose-response relationship for rectal morbidity following prostate cancer RT, initially with three large data sets (N>600), where only pre-treatment CT is available (Project 1). The robustness of these results will then be studied as a function of rectal motion in another large cohort (N>500) with daily CBCT (Project 2). In the last part, we will study rectum biomechanical properties using repeat MRI (Project 3).

The project appears to be promising due to the study of a unique large cohort of prostate cancer patients. Also comparison between cohorts will be explored, and including functional properties of the rectum could yield accurate dose-response relationships for rectal morbidity.

P27.07 Mia Møller

INCREASED SENSITIVITY OF PROSTATE CANCER DIAGNOSIS BASED ON MULTIGENE MODELS OF DNA METHYLATION AS CANCER FIELD EFFECTS

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Prostate cancer (PC) is the 2<sup>nd</sup> leading cause of cancer deaths among Danish men and the most common cancer form with ~4000 diagnoses annually. Diagnosis is based on evaluation of needle biopsies performed by a trained pathologist based on morphology and immunohistochemistry. Despite the high number of diagnoses, PC is frequently missed in the initial set of biopsies, thus in more than 15 % of patients with negative initial biopsies, PC is found in repeat biopsies. To improve PC diagnosis, the aim of this project is to evaluate DNA methylation field effects in 9 genes as a potential diagnostic tool. First, we confirmed the presence of

hypermethylation in all genes in malignant (n=48) compared to non-malignant biopsy samples (n=40) using quantitative methylation specific PCR ( $p_{\text{Bonferroni}} \leq 0.00002$  in Mann Whitney U test, AUC range 0.80-0.98 in ROC analysis). Thereafter non-malignant samples from men with (n=39) or without (n=40) cancer in other biopsies were compared. Here, methylation status of no single gene showed a significant correlation to PC. However, PC is a heterogeneous disease and a panel of markers could lead to increased sensitivity of PC diagnosis if each marker adds little but complementary information. Therefore a 4-gene model comprising HAPLN3, GSTP1, AOX1 and SLC18A2 was tested and was shown to separate the 2 groups of non-malignant samples with an AUC of 0.65 in ROC analysis (PPV = 100 %, NPV = 59.7 %). In this setting it corresponds to 12 samples of 39 that would be identified as PC samples based on the molecular analysis while not identified by pathology. Thus, this setup seems promising for DNA methylation cancer field effects as a diagnostic tool in PC.

P27.08      Ane Bundsbæk DO METFORMIN AND OTHER BIGUANIDES HAVE A ROLE IN ANTICANCER  
Iversen      TREATMENT?

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Background: The glucose/insulin lowering anti-diabetic biguanides metformin (MET) and phenformin (PHEN), which work by partial inhibition of respiration, may have antineoplastic effects. Unfortunately, nearly all studies demonstrating anticancer effects of biguanides have used non-physiological drug concentrations in vitro. The purpose of this study is to provide evidence for or against directly mediated metabolic tumor effects using in vivo achievable biguanide concentrations.

Materials and methods: To assess drug bioavailability, we developed <sup>11</sup>C labeled biguanides which allowed assessment of in vitro cellular drug uptake and, importantly, in vivo biodistribution assessment using PET scans and organ dissection. Dose-response effects of MET and PHEN on cell proliferation/viability, glucose metabolism (FDG retention) and respiration (Seahorse XF flux analyzer) were studied in vitro in a variety of tumor cell lines. Metabolic and tumor-growth effects of repeated PHEN (100 mg/kg i.p.) treatment were studied.

Results: PHEN was 100 times more potent in vitro than MET and was therefore chosen for further in vivo testing in tumor-bearing mice, and preliminary data suggests that treatment affects tumor respiration, thus leading to improved oxygenation.

Conclusion: Our data shows that biguanides affect cellular energy metabolism and proliferation in vitro. Metabolic effects of MET were typically restricted to non-physiological concentrations, whereas PHEN

may affect a broader selection of tumors at physiologically achievable concentrations. Labeling of biguanides may allow PET-based identification of patients with tumors that will respond favorably to treatment.

- P27.09      Heidi Buvarp      TUMOR CHARACTERISTICS, PATIENT REPORTED SYMPTOMS AND SUSPECTED AND FINAL DIAGNOSIS FOR 64 SARCOMA PATIENTS REFERRED TO A SARCOMA CENTER AFTER SURGERY/BIOPSY IN NON-SPECIALIST INSTITUTIONS
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- Background: Some sarcomas are referred after surgery on suspected benign tumors. This can affect the prognosis and cause large re-excisions. Knowledge about diagnostic pathways of these patients is uncertain and must be reviewed.
- Purpose: To investigate patient and tumor characteristics, patient reported symptoms, suspected and final diagnosis, and explore reasons for referral, in sarcoma patients referred after surgery in non-specialist institutions.
- Methods: Retrospective medical file review. From a previous study on 258 sarcoma patients, we identified 64 (24.8%) referred with a confirmed histological sarcoma. Medical files were reviewed for patient reported symptoms, suspected diagnosis and reasons for referral. Patient and tumor characteristics were previously collected.
- Results: 27 (42.2%) tumors were low grade, 37 (57.8%) high grade. Lipoma and fibroma/dermatofibroma were the most reported suspected diagnoses. 8 patients were suspected of other malignancies due to location (breast, testicles). For 25 patients, initial presence of alarm symptoms was described in the referral. 32 (50%) had superficial small tumors, of which 21 were suspected skin conditions. 12 of 64 patients stated that it was a second removal of a tumor in the area. 5 patients reported changes in a tumor that had been present for years.
- Conclusions: 1/4 of sarcoma patients had surgery on suspected benign tumors. For 1/3, alarm symptoms had been reported, the remaining were not detected by referral guidelines. Sarcoma should be considered even in unusual or superficial locations, also when the tumor is <5 cm. Recurring benign tumors and changes in dormant tumors should cause re-evaluation of diagnosis.

- P27.10      Mai-Britt Bjørklund Ellegaard      PATIENT-LEAD FOLLOW-UP AFTER ADJUVANT THERAPY FOR BREAST CANCER IN AN ONCOLOGICAL DEPARTMENT
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- Background: Despite lack of evidence concerning the efficacy in detection of recurrences or new primary cancers, thousands of cancer patients are each year enrolled in follow-up programs at large costs. The Danish Health and Medicines Authority has published new strategies for follow-up of cancer patients. Innovation and scientific testing of different follow-up strategies are the main emphasis in these publications.
- Materials and methods: Study 1: A cross-sectional study investigating the outcome of a standard scheduled follow-up program after adjuvant therapy for breast cancer, based on questionnaires to 120 patients combined with data from their medical records. Endpoints are breast cancer related unmet needs, patient satisfaction, fear of cancer recurrence, identification of cancer recurrence and morbidity. Study 2: Developing and evaluation of a breast cancer patient education concept in a longitudinal observation study. Outcome: questionnaire data at baseline, at the end of the program and at 6- month post intervention from 168 patients. Study 3: A randomized controlled study investigating the impact of a patient-lead follow-up program versus a standard scheduled follow-up program after adjuvant therapy for breast cancer in 247 patients. Endpoints are unmet needs, fear of cancer recurrence, patient satisfaction, detection of cancer recurrence, morbidity and health-related costs.
- Results: The study is ongoing.
- Perspectives: If a patient-lead follow program can meet the needs of the breast cancer patients, it would be possible to reduce health care costs and at the same time improve patient satisfaction and empowerment to live with their cancer diagnosis.
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- P28.01      Johanne Bach Andersen      SERIAL MONITORING OF CIRCULATING MICRORNAS IN ERLOTINIB TREATED LUNG CANCER PATIENTS
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- Background: MicroRNAs (miRNAs) are small noncoding RNAs that inhibit the translation and stability of messenger RNAs (mRNAs). They negatively regulate gene expression, and their dysregulation has been implicated in tumorigenesis. MicroRNAs are present in serum, and their role as new promising biomarkers are currently under investigation in order to contribute to a more personalized approach for the treatment of non-small cell lung cancer (NSCLC). Previous studies on cell lines and animals have

revealed that miR-30b and miR-30c influence the sensitivity of lung cancer cells to TKIs.

Aims: Are miR-30b and miR-30c predictive biomarkers of response to Erlotinib treatment? Can miR-30b and miR-30c predict resistance earlier than progression is visible by RECIST criteria?

Material and methods: Serum from 315 patients with advanced NSCLC adenocarcinoma will be analysed. The cohort consists of unselected patients treated with erlotinib, mainly in second-line, and includes patients both with and without mutations in the EGF-receptor. Serial blood samples collected at treatment start, every 4 weeks during treatment and at the time of progression will be analysed. MiR-30b and miR-30c are quantified using the TaqMan® MicroRNA Assay, and their dynamics are correlated to clinical data.

Perspectives: Circulating microRNAs can be useful markers in selecting patients to Erlotinib and in early detection of resistance development. This will spare the patients from an ineffective treatment and support the clinicians in their decisions regarding choice of drug and change of treatment.

P28.02      Line M Hybel      PREDICTION OF RADIATION INDUCED TOXICITY - PROJECT DESCRIPTION  
Schack

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Radiation therapy (RT) is an important part of cancer treatment. Late normal tissue morbidity defines the limit for dose delivery to the tumors and hence has importance for the curative potential of radiation therapy. This PhD project will focus on radiation-induced morbidity and consists of two projects. The overall aim is to develop a predictive model for which patients are more radio sensitive and which are more radio resistant.

Project 1: Candidate SNPs as Predictive Markers of Radiation-Induced Morbidity in a Prostate Cohort.

A cohort of 234 patients having received RT with curative intent has been thoroughly investigated for radiation induced morbidity by questionnaires and anal physiological analyses. These patients will be invited to donate blood samples, from which we will perform a candidate SNP study based on already published SNPs with relation to radiation-induced late toxicity.

Project 2: The Danish Radiogenomics Study for Radiation-Induced Toxicity.

A two-stage genome-wide association study (GWAS) based on buffycoats from 1000 patients treated with curative RT for head and neck cancer will be performed at Strangeways Research Laboratory, University of Cambridge. We aim to identify SNPs that are associated with the risk of developing acute or late morbidity after RT. Markers with genome-wide



significance will be tested in a 2<sup>nd</sup> stage in two validation cohorts of one thousand head and neck cancer patients and one thousand breast cancer patients, both cohorts having received curative RT. All patients have been prospectively scored for toxicity according to standardized scales from the Danish Head and Neck Cancer Group and the Danish Breast Cancer Cooperative Group.

P28.03      Katrine Rye  
Hauerslev

#### BREAST CANCER: SHOULDER DISABILITY AND LATE SYMPTOMS FOLLOWING ONCOPLASTIC BREAST SURGERY

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Background: During the last 20 years, there has been increasing focus on the morbidity following breast cancer treatment. This has led to new and less mutilating surgical techniques to replace the traditional operations: breast conserving surgery (BCS) instead of mastectomy and sentinel lymph node dissection instead of axillary lymph node dissection. Lately, oncoplastic techniques have been introduced. These techniques further increase the ability to preserve the breast and are expected to increase the cosmetic results compared to traditional techniques. They are somewhat larger procedures and might lead to increased morbidity after treatment. Hitherto this has not been evaluated in clinical research trials.

Aim: To examine if oncoplastic breast surgery techniques have an independent influence on morbidity, cosmetic result and quality of life compared to BCS.

Methods: A prospective cohort study with 18 months follow-up. Patients with breast cancer or carcinoma in situ are evaluated before BCS with or without oncoplastic techniques and 18 months later. This is done in two studies:

1. A questionnaire describing the occurrence of loco-regional morbidity. The questions regard: pain, sensibility, swelling, restrictions of movements, force, quality of life, comorbidity, body image and physiotherapy.
2. An objective evaluation of shoulder and arm function and cosmesis. It consists of the following measurements: passive range of movement, Constant Shoulder Score, sensibility, arm circumference, arm volume (by the simplified water displacement method) and cosmetic outcome.

Results: So far 39 patients have been included; 39 to the questionnaire and 15 to the objective evaluation.

P28.04      Marie Toft-  
Petersen

#### HIGH FRACTIONS OF CD34+CD38- CELLS WITH ABERRANT HMICL EXPRESSION PREDICT SHORTER OVERALL AND PROGRESSIONFREE SURVIVAL IN MYELODYSPLASTIC SYNDROME

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**Introduction:** In acute myeloid leukemia, the human Myeloid Inhibitory C-type lectin-like receptor (hMICL) has been proposed as a marker of the leukemic stem cell (LSC). Previous studies have shown aberrant marker-expression on CD34+CD38- cells in MDS, e.g. CD7, but only in minor fractions of patients. Using multicolor flowcytometry, we examined the expression of hMICL on the CD34+CD38- cells from 19 untreated MDS patients and correlated the results to follow-up data.

**Materials and methods:** Bone marrow (BM) samples were collected from 19 MDS patients diagnosed at the Department of Haematology. Normal BM (NBM) from 11 volunteers served as controls. Following lysis of red blood cells, BM was stained with anti-CD34, anti-CD3, anti-CD45 and anti-hMICL. Using the back-gating strategy, the CD34+CD38-hMICL+ cell subset was shown to cluster in an FSC-SCC plot.

**Results:** As expected, hMICL was not found on CD34+CD38- cells in NBM (0.0%) whereas aberrant hMICL expression was present on the CD34+CD38- stem cells in 16/19 (84%) of MDS cases. In MDS, the CD34+CD38-hMICL+ cells amounted a median of 5.68% (range 0.0-56.94%) of the CD34+CD38- subset. Patients with fractions of hMICL positive CD34+CD38- cells above the median (5.68%) showed a significantly shorter progression free survival compared to patients with hMICL+ fractions below the median ( $p=0.01$ ). The same trend was evident with regards to overall survival ( $p=0.06$ ). Our study identifies hMICL as a potential LSC-marker in MDS. A considerable advantage of hMICL is its complete absence on normal haematopoietic stem cells. Thus, hMICL marking of the CD34+CD38- stem cells might serve as a prognostic indicator in the future.

P28.05      Susanne  
Rylander

A DIFFERENTIAL DOSE PRESCRIPTION STRATEGY IN PERMANENT LOW-DOSE-RATE PROSTATE BRACHYTHERAPY

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**Background and purpose:** We investigated the application of a differential target and dose prescription concept for low-dose-rate prostate brachytherapy (LDR-BT), involving a re-distribution of dose according to risk of local failure and treatment-related morbidity.

**Material and methods:** Our study included 15 patients. Multiparametric MRI was acquired prior to LDR-BT for gross tumor volume (GTV) delineation. Trans-rectal US images were acquired during LDR-BT for prostate gland- (CTV<sub>Prostate</sub>) and organs at risk (OARs) delineation. The GTV contour was transferred to US images after MRI/US registration. An intermediate-risk target volume (CTV<sub>Prostate</sub>) and a high-risk target volume (CTV<sub>HR</sub>=GTV+5

mm margin) was defined. Two virtual dose plans were made: Plan<sub>risk-adapt</sub> consisted of a de-escalated dose of minimum 125 Gy to CTV<sub>Prostate</sub> and an escalated dose of at least 145-250 Gy to CTV<sub>HR</sub>, and Plan<sub>ref</sub> included the standard clinical dose of minimum 145 Gy to CTV<sub>Prostate</sub>. Dose-volume histogram (DVH) parameters were expressed in equivalent 2 Gy fractionation doses.

Results: The median D90% to the GTV and CTV<sub>HR</sub> increased by 40 Gy and 15 Gy, respectively when comparing Plan<sub>risk-adapt</sub> to Plan<sub>ref</sub>. Median D10% and D30% for the urethra decreased by 13 Gy and 14 Gy, respectively and for bladder neck by 25 Gy and 21 Gy, respectively. The median rectal D2.0cm<sup>3</sup> had a decrease of 6 Gy, while the median rectal D0.1cm<sup>3</sup> had an increase of 2 Gy.

Conclusions: Our risk adaptive target and dose prescription concept of prescribing a lower dose to the whole gland and an escalated dose to the GTV using LDR-BT seed planning is technically feasible and resulted in a dose-reduction to urethra and bladder neck.

P28.06 Mathilde Thomsen

#### CHARACTERIZATION OF TUMOR HETEROGENEITY AND CELLULAR SUBPOPULATIONS IN BLADDER CANCER PATIENTS WITH PROGRESSIVE DISEASE

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Background: Bladder cancer patients would very likely benefit from targeted treatment based on the specific driver mechanisms underlying disease progression and metastasis. When characterizing tumor specimens, the heterogenic bulk tumor is often analyzed generating "average" cellular profiles or biopsies of non-aggressive cellular subpopulations with no progressive potential may erroneously be selected for analysis.

Methods: Genomic alterations for ultra-deep targeted sequencing are selected from exome sequencing of multiple bulk tumor biopsies from bladder cancer patients undergoing radical cystectomy. Targeted sequencing will be applied to subpopulations procured by either laser microdissection (LMD) of tumor as well as lymph node metastases or flow sorted subpopulations. This may reveal the clonal hierarchy and give insight into the tumor heterogeneity to delineate driver mechanisms for the individual patient. Transcriptional heterogeneity will be investigated by Fluidigm QPCR assays and compared to genomic alterations. The functional impact of potential driver mechanisms will be assessed by in vitro studies using isogenic cell lines.

Status: 4 patients have been sampled, and tumors are being sequenced to identify genomic variants for targeted sequencing. For the initial two patients, a mean target coverage of minimum 50x was obtained. Preliminary analysis of the exome sequencing revealed 175 and 555 somatic mutations. Mutations in genes commonly mutated in bladder

cancer such as PIK3C3, and EP300 was identified along with novel mutations. Targeted sequencing of identified mutations on LMD subpopulations will hopefully give further insight into subclonal heterogeneity.

- P28.07 Peter Asdahl ESOPHAGEAL STRICTURES AMONG CHILDHOOD CANCER SURVIVORS: A REPORT FROM THE ADULT LIFE AFTER CHILDHOOD CANCER IN SCANDINAVIA (ALICCS) STUDY

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Background: Among survivors of childhood cancer, esophageal stricture has been described in several case reports as a late occurring consequence of treatment. The aim of this study was to estimate the risk and identify treatment related risk factors.

Methods: In a Nordic population-based setting, we identified 31,132 one-year survivors of childhood cancer and 207,041 comparison persons. From the nationwide hospital registries, we abstracted information on esophageal strictures. Secondly, to determine the treatment related risk factors, we are conducting a case-cohort study nested in the childhood cancer cohort. For this part of the study, we are currently collecting information on childhood cancer therapy, i.e. chemotherapy, radiation, and surgery in a randomly selected sub-cohort (N=600) and for identified cases of esophageal stricture.

Results: Eighty childhood cancer survivors developed esophageal stricture during follow-up. Based on the comparison cohort, only seven cases were expected. The relative rate (RR) gradually decreased over time from cancer diagnosis: 110 (95% confidence interval: 50-230) 1 - 4 years from diagnosis and 5 (3-7) ≥20 years from cancer diagnosis. Overall, survivors of leukemia (RR: 41 (25-68)) and lymphoma (RR: 18 (11-29)) had the highest risk of esophageal strictures. Abstraction of treatment information is ongoing, but we hypothesize that chest irradiation, anthracyclines and bone marrow transplantation increase the risk of esophageal stricture.

Conclusion: The risk of esophageal stricture is highly increased among former childhood cancer patients but is still an uncommon complication. Survivors of leukemia and lymphoma have the highest risk.

- P28.08 Anne Winther EGFR CA REPEAT POLYMORPHISM PREDICT CLINICAL OUTCOME IN EGFR  
Larsen MUTATION POSITIVE NSCLC PATIENTS TREATED WITH ERLOTINIB

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Background: Somatic mutations in the epidermal growth factor receptor (EGFR) are predictors of efficacy for treatment with the EGFR tyrosine kinase inhibitor erlotinib in non-small cell lung cancer (NSCLC). A CA repeat polymorphism in intron 1 of the EGFR gene influences the transcription of the EGFR gene. This study evaluates the association between the CA repeat polymorphism and outcome in NSCLC patients treated with erlotinib.

Materials and methods: Number of CA repeats in the EGFR gene was evaluated with PCR-fragment length analysis by capillary electrophoresis in 432 advanced NSCLC patients treated with erlotinib irrespective of EGFR mutation status. Patients were dichotomized into harboring short allele (CA  $\leq 16$  in any allele) or long alleles (CA  $> 16$  in both alleles). Number of repeats was correlated with clinical characteristic and outcome. A subgroup analysis was performed based on the somatic EGFR mutation status.

Results: In EGFR mutation positive patients (N=62), we demonstrate a significantly higher median progression free survival (HR= 0.39 (0.22-0.70); p=0.002) and overall survival (HR= 0.43, (0.23-0.78); p=0.006) in patients also harboring a short CA repeat length versus a long (median follow-up time of 52.2 months). The result remained highly significant in a multi-variate Cox proportional hazards model. This correlation was not seen in EGFR mutation negative patients.

Conclusion: Our study demonstrates that in EGFR mutation positive NSCLC patients treated with erlotinib a low number of CA repeats in intron 1 of the EGFR gene is a predictor for both longer progression free survival and overall survival.

P29.01      Mette Heisz      MELANOMA IN SITU: A SINGLE-CENTRE EXPERIENCE WITH 479 PATIENTS

Ørndrup

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Background: Treatment of MIS is a challenge due to the tendency of subclinical spread and the frequent presentation in the head and neck region in cosmetically complex areas. The aim of the present study was to explore the characteristics of MIS, including epidemiological aspects, treatment and relapse.

Methods: All patients with clinically and pathologically proven MIS diagnosed between 2000 and 2008 at Aarhus University Hospital, Denmark, were examined retrospectively. Information on treatment, clinical and histological variables and correlations between them were analyzed.

Results: 479 MIS-lesions in 478 patients were included, 63% women and 37% males, with a mean age at diagnosis of 58 years, women younger than men. Most common body site was the head and neck region (31%).

The dominant histological subtype was superficial spreading (67%) followed by lentigo maligna (32%) and acral (1%). 13 patients (3%) had local recurrence, 11 in the face. Six (46%) out of the 13 patients were excised with a margin less than 5 mm.

Conclusions: Little is known about the potential for MIS to progress to invasive melanoma. These demographic observations may contribute to understanding the behavior of this tumor, which is fundamental in deciding how aggressively the clinician should treat MIS. The majority of MIS-patients developing recurrence were treated with an excision margin less than the recommended 5 mm. This emphasizes that, despite the aesthetic challenge in treating difficult anatomical locations, the clinician must consider carefully whether it is a good idea to compromise on excision margin.

P29.02 Ditte Løhmann TOXICITY IS ASSOCIATED WITH AGE IN NOPHO-AML 2004

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Objective: Due to the high-intensity treatment of childhood, acute myeloid leukemia (AML) almost all patients experience toxicities; some life threatening. Children  $\geq 10$  years with AML experience worse outcome compared to younger children, in part due to treatment-related mortality. We investigated if severe toxicities were age-dependent in the NOPHO-AML 2004 protocol.

Materials and methods: We reviewed toxicities registered in the database of the NOPHO-AML 2004 protocol, including all protocol patients from the Nordic countries and Hong Kong and excluding patients who died within 7 days of diagnosis. For the analysis, 318 patients were included. Patients were censored at stem cell transplantation or relapse.

Results: During therapy, 88% experienced at least one grade 3 or 4 toxicity. Treatment-related mortality occurred in 4.4%. When comparing to 2-9-year-olds, sepsis was significantly more common in 10-17-year-olds (10% vs 20%). Admission to the intensive care unit (ICU) was more frequent in 10-17-year-olds and infants ( $<1$  year) (13% vs 23% and 24%, significant for 10-17). We found other noteworthy differences that did not reach statistical significance: assisted ventilation was more common in infants and 10-17-year-olds compared to 2-9-year-olds (12% and 14% vs 7.1%); creatinine and bilirubin levels were elevated to more than 3 x normal more often in infants compared to 2-9-year-olds (5.9% vs 0.8% and 8.8% vs 2.4). The only toxicity seen more often in 2-9-year-olds was central neurotoxicity (7.1% vs 1.8% for 10-17-year-olds).

Conclusion: In general, treatment for pediatric AML caused considerable toxicity. Infants and 10-17-year-olds experienced more toxicity during treatment.

P29.03 Christina Demuth FIBROBLASTS STIMULATE LUNG-CANCER CELL GROWTH AND INFLUENCE THE RESPONSE TO EGFR TARGETED TREATMENT

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The treatment of lung cancer has developed greatly during the last decade. Despite this, lung cancer remains the leading cause of cancer-related deaths worldwide. The cancer microenvironment is now generally recognised as a factor in the outcome of treatment.

In this study, we present data showing that the growth of lung-cancer cells is stimulated by co-culture with lung fibroblasts. We investigated tyrosine kinase receptors common in cancer and found an increased activation of EGFR and HER3 in the cancer cells, mediated by the co-culture. In accordance with previous studies we also found that the lung fibroblasts produce the EGFR ligand amphiregulin, which could explain this activation.

Additionally, we wanted to investigate the influence of the fibroblasts on the response of the lung-cancer cell lines to the EGFR targeting drug erlotinib. Data suggest that fibroblast-conditioned media rescue the cancer cells from treatment with erlotinib. Furthermore, it seems that the cell line with an EGFR mutation is less sensitive to stimulation by the fibroblasts compared to cell lines with wild-type EGFR. This indicates that the microenvironment is a more important factor for erlotinib-treatment outcome in EGFR wildtype cell lines, in comparison to EGFR mutated. Thus, the microenvironment might play a role in reducing the sensitivity to erlotinib of EGFR wild-type cell lines.

Our results confirm the importance of the microenvironment when studying mechanisms of growth and drug response in lung cancer. We see that lung fibroblasts increase the growth of the cancer and also seem to influence the response to EGFR-directed treatment.

P29.04 Anna Kirstine Winthereik GENERAL PRACTITIONERS' WILLINGNESS TO PAY HOME VISITS AND THE LIKELIHOOD OF THEIR PATIENTS TO STAY OUT OF HOSPITAL AND DIE AT HOME - A NATIONWIDE DANISH REGISTER-BASED COHORT STUDY

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Background: Home visits paid by GPs are positively associated with patients' possibility for dying at home, which is what most patients prefer. However, it may be a circular argument as patients who die home are more often seen by their GP. Therefore, it remains unclear if GP's general willingness to pay home visits is associated with days hospitalised and

dying at home.

**Aim:** To investigate associations between GPs' general willingness to pay home visits and days their deceased patients are hospitalised during last three months of life and their likelihood of dying at home.

**Method:** A register-based cohort study including all Danish general practices. Data on GPs and deceased patients is collected from Danish national registers from 2007 to 2011. Data on GPs' home visits is retrieved from Danish Health Services Register based on remuneration. Data on deceased patients regarding sex, age at death, time spent at hospital and place of death is retrieved from Danish national registers and combined using unique personal numbers.

GPs' willingness to pay home visits is measured as incidence rate ratio adjusted for patient population's age, sex, distance to practice and comorbidities. Associations between yearly willingness to pay home visits and number of days spent at hospital and home death will be analysed using multivariable regression models.

**Results:** Work is in progress.

**Discussion:** Strengthening basic end-of-life care to patients emphasises GPs' role. As GPs have many other tasks, it is important to gain knowledge about consequences of ways of organising their work and to support GPs in prioritising their resources. This study will clarify the importance of home visits.

P29.05      Mai  
Lykkegaard  
Schmidt

#### CLINICAL USE OF ITERATIVE 4D CBCT RECONSTRUCTIONS TO INVESTIGATE LUNG TUMOR MOTION

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4D conebeam CT (4DCBCT) is a useful IGRT modality that can provide respiratory phase resolved volumetric imaging of the thorax. However, conventional 4DCBCT reconstruction leads to severe undersampling artifacts unless the total number of CBCT projections is substantially increased. This problem can be mitigated by iterative 4D reconstruction. We present a clinical evaluation of two iterative 4DCBCT reconstruction algorithms during stereotactic body radiation therapy of lung cancer patients.

Two types of iterative 4DCBCT reconstructions were performed utilizing 1) total variation (TV) minimization and 2) optical flow (OF) based deformable registration between phases. The reconstructions were initially evaluated on a lung phantom with a moveable target insert and, subsequently, for 19 patients on 3 CBCT projection datasets previously acquired for conventional 3D CBCT scans. The tumor motion was extracted



and compared with the motion in the planning 4DCT scan.

For both phantom and patient scans, the iterative 4DCBCT reconstructions had sufficient quality for GTV delineation when the breathing period was faster than 3.5s (15/19 pts.), but not for slower breathing periods (4 pts.). The 3D tumor motion amplitude for the patients was significantly lower ( $p = 10^{-6}$ , Wilcoxon signed rank test) in the OF reconstructions (mean 4.0 mm) than in the TV reconstructions (mean 5.3 mm).

In this translational study, iterative registration-based 4DCBCT reconstruction of the thorax was demonstrated at 3 treatment fractions for 19 patients from a standard CBCT scan. The registration-based reconstruction considerably improved the image quality, and used to estimate the daily lung tumor motion.

P29.06 Lone Vedel Schøler

#### TUMOR SPECIFIC GENOMIC VARIATIONS, A BASIS FOR PERSONALIZED CRC MANAGEMENT

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Background: Colorectal cancer cells release DNA fragments into the circulation containing tumor specific DNA (ctDNA). Consequently, blood samples could in principle serve as liquid biopsies to detect the presence of cancer. Early stage CRCs are primarily treated by curatively intended surgery. However, 40% experience relapse of disease and early detection of relapse is crucial to improve outcome.

Aims: To show that monitoring tumor burden using non-invasive analysis of ctDNA provides clinical relevant information about: 1) radicality of the initial surgery, 2) impending disease relapse, and 3) response to oncological and surgical intervention in the follow-up period.

Methods: In order to identify tumor specific somatic structural variants, we have sequenced the primary tumor of 11 CRC patients from whom we have matched serial post-surgery plasma samples. Digital droplet PCR (ddPCR) assays were designed, tested, and optimized for an average of 4 SSVs per patient. These assays were then used to quantitatively determine the level of ctDNA in 4 ml serial plasma samples.

Results: ctDNA analysis detected impending relapse with an average lead time of 10 month compared to the conventional follow-up program. Importantly, no ctDNA was detected in post-surgery plasma of non-

relapsing patients. Changes in the ctDNA level in post-surgery plasma samples were consistent with the clinical disease course and conducted interventions. In conclusion, we find that post-surgery serial analysis of ctDNA has the potential to become a practice changing tool, as it creates a critical window of opportunity for intervention at time-points where curative modalities are still an option.

- P29.07      Ditte Louise Egeskov Munkedal      POST-OPERATIVE MULTI-DISCIPLINARY TEAM MEETINGS HAVE A POSITIVE EFFECT ON THE SURGICAL QUALITY IN COLON CANCER
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- Background: Over recent years, there has been a new focus on the quality of colon cancer surgery after the introduction of complete mesocolic excision (CME). The pathological evaluation of the surgical specimen emphasises a resection in the embryological plane (the mesocolic plane). This renders a specimen, which contains all possible ways for tumour spread. Aarhus University Hospital (AUH) in Denmark implemented CME surgery in 2008 after a post-graduate development course (PgDC) in 2007. After 2010, post-operative multi-disciplinary team (PO-MDT) meetings were held where pathologists demonstrated the surgical resection plane of the specimens to the surgeons.
- Aim: To evaluate the effect of PO-MDT meetings on the proportion of colon cancer specimens resected in the mesocolic plane.
- Method: The study included 209 colon cancer specimens, from patients who underwent potentially curative surgery, collected at AUH during 2008 to 2011. In a logistic regression analysis, we controlled for: age, gender, body mass index, calendar year, surgical approach, stage of disease, and tumour site.
- Results: When CME was implemented in 2008, the percentage of specimens in the mesocolic plane was high (67 %). The proportion fell in 2009 (53 %) and 2010 (52 %) but increased significantly in 2011 (76 %) ( $p = 0.02$ ) following the implementation of PO-MDT meetings in 2010.
- Conclusion: Implementation of CME is a challenge and needs continuous training even after a PgDC. The key element seems to be PO-MDT meetings.

- P29.08      Ellen Marie Høye      A NEW DOSIMETER FORMULATION FOR DEFORMABLE 3D DOSE VERIFICATION
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**Introduction:** The increasing complexity of radiotherapy demands dose verification in three dimensions with high spatial resolution. In this study, silicone has been investigated as a host matrix for leuco-malachite green dye dissolved in chloroform, in order to create a 3D dosimeter with new clinical applications. With increasing doses, the dye becomes increasingly green and chloroform functions as an initiator of this reaction.

**Materials and methods:** The dose response as well as the dose-rate and photon-energy dependence of the dosimeter were characterized. To optimize the dose-rate dependence, different concentrations of the chemical components were investigated. A cylindrical dosimeter was irradiated with a volumetric modulated arc therapy plan and read out with an optical-CT scanner.

**Results and discussion:** A significant dose-rate dependence and a small energy dependence was initially observed. Further investigations at different dye and initiator concentrations showed that the dose-rate dependence could be removed by increasing the dye concentration, but that this greatly deteriorated the stability of the dose response. The standard deviation between measured and calculated dose was 5% of the total dose for the cylindrical dosimeter. The dosimeter has physical characteristics which allows for molding the dosimeter into the desired shape and manipulating it mechanically during irradiation to mimic clinically relevant deformation of organs.

**Conclusion:** This first study of the silicone dosimeter with LMG dye shows that it has significant potential for use as a radiochromic dosimeter in clinical practice, but that further investigations and development are necessary.

P29.09      Jenny Bertholet **TARGET TRANSLATION, ROTATION AND DEFORMATION DURING LIVER STEREOTACTIC BODY RADIATION THERAPY**

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Radiotherapy should ideally maximize the ratio between tumor dose and healthy tissue irradiation. This task is complicated by intra-fraction tumor motion. Tumor tracking is a method to account for breathing induced motion of target in radiotherapy with the possibility to correct for tumor rotation. However, reliable real-time tumor position monitoring is required for tracking.

For liver stereotactic body radiotherapy (SBRT), implanted gold marker are commonly used as X-ray visible surrogates for the tumor and can be used for real-time position monitoring of the tumor.

The overall aim of this project is to obtain safe clinical implementation of image-based tumor tracking for liver SBRT through a carefully designed series of pre-clinical and clinical studies.

A method for offline calculation of the translation, rotation and deformation of a tumor from 2D Cone-Beam Computed Tomography (CBCT) projections has been developed. Preliminary results on target translation and rotation will be presented for 26 patients (198 sets of projections) undergoing liver SBRT between 2009 and 2013 at Aarhus University Hospital.

The method will be further developed for online use and applied to correct for the tumor rotation on the day of treatment. Finally, the method will be used in real-time for continuous corrections during treatment delivery by Multi-Leaf Collimator (MLC) tracking in a clinical feasibility study. The project will lead to more accurate radiotherapy with a higher ratio between tumor dose and normal tissue dose and a lower risk of partly missing the tumor. The developed tumor tracking methods will be available for any conventional linear accelerator for radiotherapy.

- P29.10      Sigrid Salling  
Árnadóttir      DEVELOPMENT OF A NOVEL ASSAY FOR MONITORING COLORECTAL  
CANCER; BY DETECTION OF KRAS AND BRAF MUTATIONS IN  
CIRCULATING TUMOR DNA

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Background: Mutations in KRAS and BRAF are common in colorectal cancer (CRC); ~ 45% of CRCs acquire such a mutation as an early step in the oncogenesis. Solid tumors, incl. CRC, release small tumor DNA fragments into the blood, so-called circulating tumor DNA (ctDNA).

Aim: To develop a blood-based digital droplet PCR (ddPCR) assay panel that enables detection and quantification of KRAS and BRAF mutations in ctDNA.

Methods: We have developed ddPCR assays for detecting 13 mutations in codons 12, 13, and 61 of KRAS and 1 assay for codon 600 in BRAF. Primers and probes contain LNAs (locked nucleic acids) to increase the specificity and to allow designs with very short amplicons (<80bp), which is necessary since ctDNA is very fragmented.

Results: All assays are highly specific and give no signal with wildtype (WT) template, despite the fact that the mutated sequences differ from WT by only one base. The assays are highly sensitive and detect down to a few mutated copies in a background of 20.000 WT sequences. We plan to determine the sensitivity and specificity of our assays by applying them to matched tumor DNA and ctDNA from patients with known KRAS and BRAF mutations.

Perspectives: This set-up provides a blood-based approach for monitoring tumor burden and mutational development, which has the potential to be used for early detection of relapse after intended curative surgery, and to monitor response to treatment.

P30.01 Rikke Madsen PATIENT AND RELATIVE EXPERIENCES CONCERNING TRANSITIONS FROM A COURSE OF INCURABLE CANCER

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Background: In 2008, 7.6 million people, worldwide, died from cancer. It is projected that in 2030, 13.1 million people will die from cancer. Studies have identified that patients and relatives experience difficult transitions during the course of incurable cancer. However, more in-depth knowledge is needed to illuminate the life world experiences of transitions from the perspective of both patients and relatives.

Aim: To explore lived experiences from everyday life, related to transitions during the course of incurable cancer, through the perspective of patients and bereaved spouses. In this study, transitions are conceptualised as experiences concerning organisational, psychosocial and existential issues

Method: Data will be collected through four sub-studies: 1. A systematic literature review (April-August 2013, October 2014 - January 2015), 2. Field observations (Conducted January - June 2013), 3. Interview of ten incurable cancer patients (2015), 4. Interview of ten bereaved spouses (2015).

The systematic literature review will provide an overview of findings from existing qualitative research. Field observations will result in developing an interview guide for the semi-structured interviews. Data from interviews will be analysed using Ricoeur's phenomenological-hermeneutic theory of interpretation focusing on meaning units from the life world experiences of the participants. The interviews will generate in-depth knowledge from the life worlds of incurable cancer patients and bereaved spouses on a topic, which has not previously been carried out.

P30.02 Yuduo Zheng TOXICITY OF SILVER NANO-PARTICLES AND ULTRAFINE COMBUSTION PARTICLES ON A549 CELLS

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Introduction: Silver nano-particles (AgNPs) are extensively used in products. Although exposure through inhalation is not common, it may occur in occupational setting. Ultrafine combustion particles (UfCPs) are the main source of particles with a diameter of 2.5 µm or less (PM<sub>2.5</sub>) in environment.

Material and methods: Cubic AgNPs (CAgNPs) and spherical AgNPs (SAgNPs) were synthesized, purified and characterized. Eight kinds of combustion particles were collected during car driving (6 engine exhaust samples) or wood burning (2 wood smoke samples). On day 1, A549 cells were seeded into 6- or 24- well plates, and grew for 24 h. On day 2, cells were exposed to particles at a concentration of 100 µg/mL for 24 h. On day 3, cells were collected for analysis of reactive oxygen species (ROS) generation, and cell culture medium was collected for analysis of cytokines (mainly interleukin 8 (IL-8)) secretion. So far, both kinds of AgNPs were tested repeatedly. A preliminary test with 4 (2 engine exhaust and 2 wood smoke) out of the 8 UfCPs was done.

Results: Both CAgNPs and SAgNPs increased ROS formation and IL-8 secretion. SAgNPs might be slightly more toxic to A549 cells than CAgNPs. All 4 UfCPs increased IL-8 secretion, but only 3 of them increased ROS formation (one engine exhaust sample did not). Wood smoke might be more toxic to A549 cells than engine exhaust.

P30.03      Sara Francis      IDENTIFICATION OF THE SPOUSE'S RESPONSIBILITIES, FUNCTIONS AND ROLES IN RELATION TO CARE FOR A LOVED ONE WITH A PRIMARY BRAIN TUMOUR

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Background: Being a spouse to a loved one with a primary brain tumour can be an overwhelming and stressful experience as the patient can suffer from severe multiple neurological and cognitive symptoms. These can be physical disabilities, memory loss, impaired intellect or a change in personality. Because the patient cannot fulfil the role and functions they normally have, the spouse can be forced to take on a number of new and different responsibilities. They often have to adopt various functions related to helping the patient through the disease and treatment to maintain the patient and the family's way of life.

Aim: The aim of the project is to identify the spouse's responsibilities, functions and roles in relation to care for a loved one with a primary brain tumour, so the necessary and appropriate support can be tailored to the spouse's individual resources and special needs.

Methods: Qualitative research interviews will be carried out with 10 spouses of recently diagnosed patients midway through the initial treatment and two months after treatment. A further 10 qualitative interviews will be carried out with experienced spouses later in the course of the disease.

Perspectives: The project will contribute with knowledge about what kind of support these spouses require when and by whom in a multidisciplinary and cross-sectorial perspective. In other words, what is best for whom and when? This is to improve cooperation between the patients, spouses and healthcare professionals in order to provide security and help and to

P30.04	Jesper Beck Jørgensen	MESORECTAL EXCISION FOR RECTAL CANCER: ASPECTS OF RECURRENCE AND SURVIVAL
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The purpose of this study is to evaluate whether the quality of surgery, as evaluated by MRI three years after surgery, is associated with the risk of LR. Further, to evaluate whether the present treatment regimen of proximal rectal cancer is oncologic safe, and similarly for distal rectal cancer managed with abdominoperineal excision (APE). The different modalities of rectal surgery (PME, TME and APE) will be compared regarding 3-year LR rates and 5-year survival. Further we aim to illuminate the extent of defunctioning stoma use in case of mesorectal excision surgery in Denmark and examine the data validity of the Danish Colorectal Cancer Group register.

**Background:** Accurate quantitative and qualitative evaluation of disease status is important in non-small cell lung cancer (NSCLC) patients in order to recognize ineffective treatment or relapse. Serial imaging and tumor biopsies are widely used, but supplementary information could be obtained non-invasively by analysis of circulating DNA fragments in the

bloodstream carrying tumor-specific mutations (ctDNA).

Aim: To assess the longitudinal correlation between dynamics in radiographic tumor burden and ctDNA.

Methods and materials: Pre-treatment plasma samples from 150 patients with stage I-IV NSCLC will be screened for a panel of 15 common somatic NSCLC mutations by the use of highly sensitive ASB-PCR assays. The mutations detected in each case will be used to track the quantitative dynamics in ctDNA during periods of treatment with chemotherapy, targeted therapy and/or radiotherapy or during periods of follow-up. The results of the quantitative ctDNA analysis will be correlated to the clinical and radiological data regarding disease status.

Perspectives: Dynamics in ctDNA can serve as a non-invasive real-time liquid biopsy that can supplement serial imaging in clinical decision-making regarding response to therapy or impending relapse. Patients can be spared for ineffective and often toxic treatment, and intensified follow-up with serial imaging can be initiated if ctDNA analysis reveals signs of impending disease progression or relapse. The impact on overall survival of this novel approach has to be assessed in randomized trials.

P30.06      Anne Ramlov      RELATIONSHIP BETWEEN LYMPH NODE DOSE AND NODAL OUTCOME IN LOCALLY ADVANCED CERVICAL CANCER

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Relationship between lymph node dose and clinical outcome in locally advanced cervical cancer.

Purpose: To investigate the relationship between dose, volume and clinical outcome for metastatic lymph nodes in locally advanced cervical cancer.

Materials and methods: A total number of 140 patients treated at either Aarhus University Hospital (AUH) or University Medical Center Utrecht (UMCU) were included in this study. For the 74 node positive patients with a total of 219 nodes, each metastatic node was delineated separately on the planning CT scan. For each node, the total dose was calculated as the dose delivered by external beam radiotherapy (EBRT) + nodal boost given as either a sequential EBRT boost or a simultaneous integrated boost (SIB) + dose contribution from brachytherapy.

Results: Median dose to all boosted nodes was 62.3 Gy (range 45.1-69.1 Gy). Median volume of all nodes was 1.4 ml. (range 0.1-44.9). Five boosted nodes recurred giving a nodal control rate of 97.7%. Five patients (6.7%) had a recurrence in a boosted node. For boosted nodes with recurrence, the median nodal dose was 62 Gy. Five patients (3.6%) had a recurrence in the elective nodal area. Ten patients (7.1%) had a nodal recurrence outside the field in the para-aortic (PA) area. Four of the patients with PA



recurrence did not have nodal disease at time of diagnosis.

Conclusion: Nodal control rate in locally advanced cervical cancer is quite high. Recurrences in para-aortic nodes are the most common site of recurrence.

P30.07      Line Brøndum      PLASMA MARKERS IN HEAD AND NECK CANCER IN CORRELATION TO FAZA PET CT AND A HYPOXIC GENE PROFILE

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Background: Hypoxia and HPV are important factors for radioresistance in head and neck cancer. However, methods for identifying hypoxia are warranted. A hypoxic gene profile has been developed to predict the benefit of hypoxia modifying treatment. In a prospective clinical trial, FAZA has been characterized as a hypoxic PET marker.

Aim: To identify possible predictive and prognostic markers of hypoxia in the blood of head and neck cancer patients and to correlate the markers to tumor hypoxia assessed by the hypoxic gene profile and FAZA PET CT and to tumor HPV-status. Additionally, we establish the normal levels of these factors in matched control subjects.

Materials and methods: Baseline plasma samples from 27 head and neck cancer patients and 18 gender and age matched controls were analyzed for 19 different proteins. The HPV-status of the patient tumors was assessed.

Results: We found significantly higher factor levels in the patient plasma samples regarding VEGFR-1, VEGFR-2, II-6, II-8, PAI-1, leptin, OPN, EGFR, eotaxin, VEGF and HGF compared to the control group. The factors elevated in the patient blood samples compared to the control samples have the highest concentrations in the HPV-negative group (P=0.003). When comparing the factors in the blood with the patients classified as hypoxic according to the hypoxic gene profile, there is a trend that the patients with the highest levels of the factors are significantly overrepresented in the group classified as hypoxic according the gene profile. No correlation was found with the FAZA PET CT scans.

Conclusion: By exploring the heterogeneous nature of hypoxia, we aim to tailor biologically adapted individualized treatment.

P31.01      Anna Sundby      WHOLE GENOME SEQUENCING - NEW POSSIBILITIES, NEW DILEMMAS

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Background: In 2007 the first individual genome was sequenced for research purposes and whole genome sequencing (WGS) is rapidly emerging as important tool in human genetics research. WGS has made it possible to identify genetic variations for many disorders but makes it possible to identify genetic variation unrelated to the primary focus of the research.

**Methods:** We made a pilot study including 9 interviews with genetic researchers and patients with schizophrenia and 4 focus group interviews with clinical geneticists, relatives of psychiatric patients, patients with ADHD and blood donors.

Next step: We have translated and modified a web-based questionnaire designed by the Wellcome Trust Sanger Institute to examine the attitudes to WGS research in a Danish context. Potential research subjects were invited to complete the questionnaire in August 2014.

P31.02	Monica Milter Ehlers	A SYSTEMATIC REVIEW OF QUALITATIVE AND QUANTITATIVE STUDIES 2001 - 2014
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**Aim:** The objective of the study was to evaluate knowledge about functioning and disability of postoperative hip fracture patients older than 65 years.

Background: There is limited knowledge about how patients older than 65 years characterise and experience their functioning and disability after hip fracture surgery.

**Methods:** A systematic literature search was conducted in electronic databases. 24 scientific papers published between 2001 and January

2014 met the inclusion criteria. The papers were critically appraised according to the Joanna Briggs tools for critical appraisal and data extraction. 14 papers were selected for the final review and underwent a data extraction in order to identify relevant areas and findings.

Findings: Preliminary findings show that hip fracture patients often develop depression and confusion as a result of the fracture, pain, anxiety and impaired cognitive function. Patients experience pain at rest and after mobilisation post discharge from hospital. More than half of the hip fracture patients are dependent on help in order to perform P-ADL, which affects their sense of independence and quality of life.

Conclusion: The existing literature offers an insight into the characteristics of hip fracture patients and how the patients experience change in body function, activity level, participation, the environment, life, and living.

Practice implications: Further research-based knowledge is needed to explore a) How health care professionals assess patients' functioning, disability, and rehabilitation and b) How patients and their close relations have experienced patients' functioning, disability, and rehabilitation.

- P31.03      Jakob Søgaard THE USE OF IMMUNOCHEMICAL FAECAL OCCULT BLOOD TEST (iFOBT) IN  
Juul                      GENERAL PRACTICE. A STUDY OF PARTICIPANTS IN SCREENING, THE  
IMPLEMENTATION OF iFOBT IN GENERAL PRACTICE AND THE RISK OF  
COLORECTAL CANCER IN CASE OF NEGATIVE iFOBT

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Background: Colorectal cancer (CRC) is common and a leading cause of cancer death. The evaluation of patients suspected to have CRC is difficult due to poorly predictive alarm symptoms, and many patients present with uncharacteristic or vague symptoms. The faecal marker of human globin, iFOBT, could play an important role in aiding the general practitioner in detecting CRC.

Aims: 1. to investigate the use of health care services in general practice, for patients invited to and participating in CRC screening, three years prior invitation, 2. to develop a guideline for the use of iFOBT in general practice, and evaluate upon the implementation of iFOBT and guideline in general practice and 3. to investigate the possibility of having CRC when criteria of fast-track referral for CRC are met, but iFOBT is negative.

Materials and methods: The study will consist of three substudies.

1. Patients invited to screening for CRC are divided into cohorts of

participants and non-participants. Participants are further divided into positive vs. negative iFOBT and CRC vs. no CRC. Cohorts are compared regarding use of health-care services in three years leading up to invitation.

2. A guideline for the use of iFOBT in general practice is developed. General practices in the Central Denmark Region are randomised to use iFOBT and will receive continuous medical education in the use of the test. After the study period, the implementation of guideline and iFOBT will be evaluated.

3. Patients referred to fast-track evaluation of CRC are invited to perform an iFOBT prior to colonoscopy. Result of iFOBT is compared with result of colonoscopy, and the risk of having CRC in case of negative iFOBT is estimated.

P31.04 Marie Tvilum Petersen THE CLINICAL IMPLICATION OF INTRODUCING ADAPTIVE RADIOTHERAPY IN THE TREATMENT OF LUNG CANCER PATIENTS

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Introduction: In April 2013, Aarhus University Hospital introduced a new adaptive strategy with tumour match when treating locally advanced lung cancer patients with curative intended radiotherapy. With this new strategy, a Cone Beam CT-scan is acquired before each treatment. By using this, the actual anatomical localization of tumour can be detected and used to position the patient precisely with respect to the beams. The scan is also used to detect relocation of tumour and lymph nodes, which may lead to a rescanning and a new treatment plan. The implementation of the adaptive strategy leads to a reduction of treatment margins and thus the region irradiated to a high dose. It is believed that this will decrease the toxicity of the treatment without increasing the incidence of marginal failure, but the clinical evidence of this is lacking.

Aim: The study aims to examine the clinical effect of an adaptive strategy and tumour match in the radiotherapeutic treatment of lung cancer patients at Aarhus University Hospital.

Methods: Clinical descriptions of fifty consecutive patients that underwent curative intended treatment after the implication of adaptive strategy will be elaborated. Fifty consecutive patients that received treatment without the adaptive strategy will be included in a control group. Relevant information will be extracted from patient journals. Clinical signs of progression and toxicity related to the treatment will be focal points. Marginal failure will be analysed by comparing the therapeutic PET/CT-scan with the CT-scan where the relapse was detected.

Perspective: The results could have an impact on the strategy of choice when treating with radiotherapy in the future.

- P31.05 Peter Sinkjær Kenney NASAL FILTERS APPEAR USEFUL IN PREVENTING SEASONAL ALLERGIC RHINITIS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CROSSOVER CLINICAL TRIAL

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Background: Nasal Filters may be useful as a preventative method for managing seasonal allergic rhinitis.

Objective: To evaluate the efficacy, safety and usability of nasal filters (Rhinix) in preventing seasonal allergic rhinitis.

Methods: This trial was a single-centre, randomized (1:1), double-blind, placebo-controlled crossover clinical trial (NCT01699165) conducted in an environmental exposure unit (EEU) in Denmark avoiding the normal grass season. Twenty-four adult subjects with a history of grass pollen-induced allergic rhinitis were included. Assessments were made by using a total nasal symptom score (TNSS). The primary outcome measure was the difference between placebo and active nasal filters evaluated by using maximum TNSSs (the highest score of the 9 ratings). Differences in daily TNSSs (the sum of all 9 ratings) were also evaluated as a prespecified outcome measure.

Results: Rhinix reduced daily TNSS by 21% (P=0.049), daily sneezing by 45% (P=0.01), maximum itching by 46% (P=0.004) and maximum sneezing by 38% (P=0.001) when compared to placebo. Rhinix failed to show a significant reduction in the primary efficacy endpoint of difference in maximum TNSS (P=0.14) with a mean reduction of 14% and median reduction of 33% when compared to placebo.

Conclusions: On the basis of the findings of this small, limited in length and exposure levels EEU trial conducted in a clinical setting, Rhinix appears useful for managing seasonal allergic rhinitis, although in-season studies on efficacy and usability (particularly concerning convenience, comfort, and treatment costs) in larger populations are needed to verify this.

- P31.06 Louise Stride Nielsen CHEMICAL FINGERPRINTING OF ILLEGAL DRUGS

*L.S. Nielsen*

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Many are familiar with the use of DNA and fingerprints in the investigation of criminal matters. These techniques are recognized in order to link suspects to the physical evidence found at a crime scene. Illegal drugs cannot be directly associated with a person. However, a comparison of the chemical composition of the illegal drugs can contribute with important

evidence in a forensic investigation. In addition to the active component, such as cocaine, heroin or amphetamine, an illegal drug is composed of several other closely related chemical substances, called impurities. These impurities comprise a "chemical fingerprint", which is unique for each batch of illegally produced drug. Using analytical techniques such as gas chromatography interfaced with a mass spectrometer and mathematical models, the chemical fingerprints can disclose a story about the drug, thus contribute with information about whether different quantities of drugs seized by the police come from the same production.

At present, the police request chemical profiling in cases with specific suspicion of link between two or more samples. However, the prospects of chemical profiling go beyond these so-called case-to-case comparisons. By analyzing and processing a larger number of illegal samples, information about dealer network, geographical distribution and turnover rates of illegal drugs can contribute to other types of police investigation.

The aim of this PhD project is to increase the use of this type of strategic analysis as the information is objective and often complementary with intelligence from, for example, telephone tapping and personal monitoring.

P31.07      Yan Zhou

#### REPROGRAMMING OF MCADD PATIENT FIBROBLAST INTO INDUCED PLURIPOTENT STEM CELLS USING A LENTIVIRUS-BASED GENE DELIVERY

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Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCADD) is one of the most common defects in fatty acid oxidation. MCADD is caused by a prevalent homozygous mutation (Lys329Glu). This mutation can lead to metabolic disorders and damage in heart, liver, and skeletal muscle systems. Previous understanding of the molecular and cellular consequence of MCADD was derived from studies of fibroblasts in vitro. However, studies of fibroblast are limited to mimic mutation effects. Induced pluripotent stem cells (iPSCs) derived from MCADD patient fibroblasts, followed by differentiation into functional cardiac, hepatic and muscular cells, will serve as better cellular models for understanding MCADD pathogenesis. In this study, we firstly established a lentivirus-based reprogramming method, which delivers a polycistronic cassette of four transcription factors (OCT4, KLF4, SOX2, C-MYC). The reprogramming vector is labeled with a red fluorescent marker dTOMATO, which enables real-time monitoring the transduction process as well as the silencing of exogenous genes. Next, to generate MCADD-iPSCs, we have isolated stem cell-like colonies which were positive for Alkaline Phosphatase, Oct4 and Nanog staining. However, we observed abnormal karyotype in some MCADD-iPSCs. Further characterizations including qPCR, differentiation and teratoma assays will be performed for the iPSCs with normal karyotype. These results provide the foundation for MCADD-iPSCs differentiation into functional cardiomyocytes, hepatocytes and skeletal

muscle cells. Mitochondrial functioning assay, proteomics, and RNA sequencing will be conducted to elucidate the physiological and molecular effects of MCADD mutation.

- P31.08 Rasha Abdelkadhem Al-Saaidi GENOME ENGINEERING OF THE CARDIOMYOCYTES-SPECIFIC MYOSIN HEAVY CHAIN GENE (MYH6) USING THE RNA-GUIDED CRISPR/CAS-9 SYSTEM TO FOLLOW CARDIAC DIFFERENTIATION

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Dilated cardiomyopathy (DCM) is a disease of the heart muscle characterized by cardiac chamber enlargement and reduced systolic function of the left ventricle. The clinical symptom of DCM is heart failure, which is often associated with arrhythmia and sudden death. DCM represents the most frequent form of all cardiomyopathies and mutations in the LMNA gene represent the most frequent known genetic cause of DCM. The mechanisms how LMNA mutations affect cardiomyocytes leading to DCM are poorly understood since myocardial tissue from affected patients remains a limited source for research purposes. In the present project, we want to generate and use patient-specific cardiomyocytes as a cellular model for investigations of the molecular disease pathology in DCM caused by LMNA mutations. Therefore, we used the clustered regularly interspaced short palindromic repeats/Cas-9 (CRISPR/Cas-9) system to follow differentiation of induced pluripotent stem cells (iPSCs) into cardiomyocytes by fusing the green fluorescent protein (GFP) to the chromosomal cardiomyocyte-specific gene myosin heavy chain 6 (MYH6). This technology enables isolation of cardiac-specific cells based on the MYH6- GFP marker. The CRISPR/Cas-9 system will greatly accelerate and simplify the identification and selection of the differentiating cardiomyocytes.

- P32.01 Laura Ozer Kettner PARENTAL SUBFERTILITY AND EPILEPSY IN THE CHILD: A STUDY FROM THE AARHUS BIRTH COHORT

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Background: Studies have indicated that children conceived by fertility treatment are at increased risk of epilepsy. However, Sun et al. showed that

this might not be due to the treatment itself but to the underlying parental subfertility.

Aim: To investigate whether children of subfertile couples not undergoing fertility treatment are at increased risk of epilepsy in childhood.

Materials and methods: The study population consisted of children and mothers recruited to the Aarhus Birth Cohort from 1995 to 2014. Using a questionnaire, the pregnant women reported information about time to pregnancy, fertility treatment and maternal characteristics. Birth characteristics were registered by the midwives attending the birth. Children with epilepsy were identified by linkage to the Danish National Patient Register and the Danish National Prescription Register. Likewise, mothers with epilepsy were identified and this information was included in the model as a potential confounder. Information on emigration or death of the children was obtained from the Civil Registration System in order to obtain the time at risk for each individual child. Data was analyzed using Cox proportional hazards regression while adjusting for potential confounders.

Results: Estimates of the association between subfertility and epilepsy in the child will be presented at the PhD Day.

P32.02      Jette Lauritzen    THE MEANINGFULNESS OF PARTICIPATING IN SUPPORT GROUPS FOR INFORMAL CAREGIVERS OF OLDER ADULTS WITH DEMENTIA: A QUALITATIVE SYSTEMATIC REVIEW

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Introduction: Support groups are considered an effective and economical way to relieve informal caregivers stress and burden. Research shows that participating in support groups seems to be beneficial for the informal caregivers, but there are no significant improvements in feelings of stress and burden. It is unclear how support groups can produce a meaningful and optimal outcome for the informal caregivers.

Aim: To identify the meaningfulness of participating in support groups for informal caregivers of older adults with dementia living in their own home.

Method: A systematic literature review based on a peer-reviewed and published review protocol was conducted. 233 full-text papers were assessed for eligibility. Five qualitative papers were selected and assessed for methodological quality prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute



Qualitative Assessment and Review Instrument (JBI-QARI). Qualitative research data were extracted and the findings were pooled, which involved the aggregation of findings to generate a set of statements that represent that aggregation, through assembling the findings rated according to their quality, and categorizing these findings on the basis of similarity in meaning. These categories were then subjected to a meta-synthesis that produced a single comprehensive set of synthesized findings that can be used as a basis for evidence-based practice.

Preliminary result: The findings indicate that, through comparing and sharing negative and positive emotions, the members of the support group are able to take on and maintain the role as caregiver.

- P32.03 Christine Ladegaard Geyti
- SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS ASSOCIATED TO POOR MENTAL HEALTH IN 30-49 YEAR-OLDS
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- Department of Public Health, Aarhus University
- Background: Poor mental health has human costs and costs to the society. To improve mental health, it is necessary to identify the characteristic of people with poor mental health.
- Aim: The aim is to identify the socio-demographic and clinical profile for 30-49 year-olds with poor mental health in Randers Municipality.
- Methods: Study design: Cross-sectional study. Population: 5261 randomly selected 30-49 year-olds in Randers municipality invited to a general health check, called "Check your health" in 2012-13. The general health check is performed in Randers Health Center with a subsequent consultation with the general practitioner. Measures: Mental health: The mental component summary score (MCS) of a questionnaire (SF-12) achieved from "Check your health". Poor mental health is defined as MCS<35.76. Socio-demographic data: Educational level, employment and support allowance, social security, early retirement. (Statistics Denmark). Clinical health data: Self-rated health, risk of fatal heart disease, alcohol consumption, and smoking. ("Check your health"). Proxy measures for psychiatric disease: Prescription of antidepressive drugs, diagnostic test in primary care, conversational therapy in primary care, and contacts to psychologist in the year prior to inclusion (national registers).
- Results: The results will be presented at the PhD Day 2015.
- Perspectives: This study is the first part of a PhD-project evaluating mental health in "Check your health". Further studies will evaluate if a focus on mental health in a general health check setting involving the municipality and the general practitioners can increase the mental health among 30-49 year-olds.

- P32.04 Marianne Eg
- MAPPING THE NATIONAL TREATMENT FOR OBESE CHILDREN AND

ADOLESCENTS IN DENMARK. A QUESTIONNAIRE STUDY OF 19 DANISH  
PAEDIATRIC WARDS.

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Background: Over the past 30 years, the number of obese children and adolescents has tripled. One in five Danish children aged 0-17 is obese. Obesity may have serious psychological and social consequences for affected children and their families. Obesity can lead to medical complications and disorders such as hyperlipidaemia, fatty liver, increased blood pressure, osteoarthritis, back pain, reduced glucose tolerance and increased risk of type 2 diabetes. The risk of developing complications is present as early as childhood or early adulthood and can in severe cases shorten the child's life. There are many different treatment programmes for obese children and adolescents in Denmark; however, an overview of the specific content and outcome of the treatment available is lacking.

Method. As part of the PhD study, a questionnaire study has been conducted mapping the treatment offered in Denmark to obese children, adolescents and their families. The questionnaire was designed for the purpose and consisted of 58 questions. Telephone interviews based on the questionnaire were conducted in the summer of 2014 by the same interviewer.

Results: All 19 Danish paediatric wards participated in the study with a response rate of 100%. Descriptive analyses are being conducted and will be analysed based on guidelines for obesity treatment recommended by the Danish Paediatric Society.

Perspectives: The study will show how and to what extent the current treatment of obese children and adolescents in Danish paediatric wards correlates with national guidelines and recommendations. The study will seek to increase the quality and standardise the treatment of obese children and adolescents in Denmark.

P32.05      Linn Berger      GENITAL MALFORMATIONS IN BOYS IN RELATION TO GESTATIONAL RISK  
                 Håkonsen      FACTORS AND FETAL GROWTH RESTRICTION

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Background: The etiology behind genital anomalies in boys is largely unknown. The most consistently reported predictors are prematurity and low birth weight, and we hypothesise that fetal growth restriction is involved in the underlying causal path. Several gestational factors predispose to adverse fetal growth, and this PhD project will explore these

further.

Objective: The aims of the PhD project are 1) to investigate maternal diabetes mellitus and thyroid diseases, including medication use and disease control and the risk for genital malformations, 2) to study fertility treatment as a potential risk indicator for genital malformations and 3) to study fetal growth restriction and placental insufficiency, assessed by ultrasound measures and measures of placental function and the risk of genital malformations.

Methods: The studies will be conducted on a registry-based population of singleton live born boys born in Denmark during 1977-2012. By using healthcare registries in combination with the large birth cohorts, The Danish National Birth Cohort, Aarhus Birth Cohort and Healthy Habits for Two, population based follow-up studies will be performed. The LABKA database with information on blood sample analyses will be used to obtain information on measures of disease control during pregnancy. For studies on fetal growth and placental function, we will use data from the Astraia database and the Danish Fetal Medicine Database.

Perspectives: We hope to uncover and clarify preventable gestational risk factors. Also, we aim to extend the insight of the underlying causality of the well-known association between low birth weight and genital anomalies by studying fetal growth more directly.

P32.06      Susanne  
Hvolgaard  
Mikkelsen

#### MATERNAL PRE-PREGNANCY BMI AND ADHD SYMPTOMS IN THE OFFSPRING

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Background: An association between maternal pre-pregnancy BMI and ADHD symptoms in the offspring has repeatedly been found. However, the neurocognitive processes underlying this relationship are not known.

Objective: To study whether maternal pre-pregnancy BMI is related to ADHD symptoms and co-morbidity in the offspring. Furthermore, we aimed to test if the association between maternal pre-pregnancy BMI and ADHD is stronger among preterm children compared to term children.

Methods: We examined the association between maternal pre-pregnancy BMI and ADHD/ADHD-comorbidity in offspring using data from three population-based birth cohorts in Denmark (Aalborg-Odense Birth Cohort, Aarhus Birth Cohort and Danish National Birth Cohort). The cohorts have been followed prospectively from early gestation and children aged between 7 and 21 years were assessed using the Strengths and Difficulties Questionnaire (SDQ). Logistic regression was used to examine maternal pre-pregnancy BMI in relation to ADHD symptoms and comorbidity in the offspring. The degree of confounding was assessed by a comparison of the associations between maternal and paternal BMI, respectively, and ADHD symptoms.

Results and conclusion: Will be presented at the PhD Day.

P32.07      Signe Timm      PLACE OF UPBRINGING IN EARLY CHILDHOOD AS RELATED TO INFLAMMATORY BOWEL DISEASES IN ADULTHOOD - A POPULATION-BASED COHORT STUDY IN NORTHERN EUROPE

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Background: Inflammatory bowel diseases (IBD), such as ulcerative colitis and Crohn's disease, have increased rapidly during the 20<sup>th</sup> century, but the aetiology is still poorly understood. Impaired immunological competence due to decreasing biodiversity and altered microbial stimulation is a suggested explanation.

Objective: Place of upbringing was used as a proxy for the level and diversity of microbial stimulation to investigate the effects on the prevalence of IBD in adulthood.

Methods: RHINE III is a postal follow-up questionnaire of the ECRHS cohorts established in 1989-1992. The study population was 10,864 subjects born 1945-1971 in Denmark, Norway, Sweden, Iceland and Estonia, who responded to questionnaires in 2000-2002 and 2010-2012. Data were analysed in logistic and Cox regression models taking age, sex, smoking and BMI into consideration.

Results: Being born and raised on a livestock farm the first 5 years of life was associated with a lower risk of IBD compared to city living in logistic (OR 0.54, 95%CI 0.31;0.94) and Cox regression models (HR 0.55, 95%CI 0.31;0.98). Random-effect meta-analysis did not identify geographical difference in this association. Furthermore, there was a significant trend comparing livestock farm living, village and city living (p<0.01). Sub-analyses showed that the protective effect was only present among subjects born after 1952 (OR 0.25, 95%CI 0.11;0.61).

Conclusion: This study suggests a protective effect from livestock farm living in early childhood on the occurrence of IBD in adulthood, however, only among subjects born after 1952. We speculate that lower microbial diversity is an explanation for the findings.

P32.08      Ingrid Nilsson      PARENTS' EXPERIENCES OF EARLY POSTNATAL DISCHARGE

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Objective: The aim of this study is to investigate new parents' experiences of being discharged early.

Design: A meta-synthesis of 10 qualitative studies was conducted using Noblit and Hare's method of meta-synthesis development.

Setting: Qualitative studies performed in western countries during 2003-2013 were included.

Participants: The 10 included studies counted 237 mothers and fathers, primiparous (first time) as well as multiparous parents.

Findings: We identified four overlapping and mutual dependent themes reflecting the parents' experiences of early discharge: Feeling and taking responsibility; A time of insecurity; Being together as a family; and Striving to be confident. Their experiences were closely related to the process of becoming a parent and influenced of how early discharge was organized and managed.

Key conclusions and implications for practice: Having the opportunity to be together as a family influenced the parents' experiences of responsibility, security and confidence in the parental role positively. When the postnatal care involved both parents and time of discharge was in agreement with the parents, it impacted the parental confidence and responsibility. Individualized available support focused on developing and recognizing the parents' own experiences of taking care of the baby increased their sense of being capable of managing the responsibility for their baby.

Taking responsibility for the baby, feeling secure and confident in their parental role was closely connected to the process of becoming a parent. Early postnatal discharge might influence the initial process positively or negatively according to the way postnatal care is organized and managed.

P32.09      Susan Larsen      UNPLANNED ADMISSION IN HAEMATOLOGY: A QUANTITATIVE AND QUALITATIVE STUDY ON EXTENT, CAUSE AND IMPACT ON PATIENT'S LIFE

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Background: Research suggests that chemotherapy treated patients at home have unmet needs and unnecessary suffering during their chemotherapy cycles, which may lead to unplanned admissions. Knowledge of the factors causing admissions is important to adjust care

and support, and prevent unplanned admission.

**Aims:** This study aims 1) to describe the extent and causes of unplanned admissions, 2) to explore and understand the impact that unplanned admissions have on patients' lives and 3) to resolve possible initiatives that prevent unplanned admissions. The aims are achieved through a quantitative and a qualitative approach. Results from study 1 will guide selection of patients for the inquiry in study 2.

**Methods:** Study 1: During a 1-year period, all unplanned admissions are registered. Data describing: socio-demographics, sickness and treatment, patient condition, nursing problems, contact to primary care facility and time, are collected and analyzed with descriptive statistics. The goal is to identify patterns and groups of patients, and the symptoms and problems leading to admission. Progress on the data collection will be presented. Study 2: Data are collected by semi-structured interviews focusing on: Patients experience of the admission and impact on patient's life. Symptoms: Before, during and after admission and dealing with these in daily life. Transition/change - Vulnerability: Patient's perception of disease and health status. The goal is to get a picture of the strategies used by patients to avoid admission.

**Perspectives:** The combination of results from studies 1 and 2 will provide new knowledge about unplanned admissions and will serve as a basis in the development of interventions that may prevent these admissions.

P32.10 David Rurik  
Martinsson

#### CHILD AND ADOLESCENT OCD SYMPTOM PATTERNS: A FACTOR ANALYTIC STUDY

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**Objectives:** To investigate OCD symptom structure in children and adolescents in order to identify OCD subtypes. A few studies have tried to identify symptom based subtypes of OCD in Children and Adolescents, and found it to contain 4-5 factors. There are several reasons for the different number of factors found such as different methods and limited sample sizes. Therefore, this study based on a large sample will be a valuable addition to the previous studies.

**Methods:** Exploratory factor analysis will be applied to the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) symptom checklist items in

order to reveal any latent factor structure. The relation between specific factors, demographics and co-morbid disorders will be examined. Data for 780 children and adolescents with OCD is already collected and the final sample is expected to be around 850 subjects, collected from 24 different research units in Denmark, Sweden, Norway, Holland and USA. This study is a part of the Nordic Long-Term OCD Treatment Study (NordLOTS).

Results: Work in progress. Preliminary results will be available at the time of presentation.

Discussion: Our study is unique in that it includes individual CY-BOCS checklist items, and it is thus possible that our results will refine or go beyond the "classical" factors in the original publication. The importance of our findings for studies on OCD genetics and pathogenesis of symptoms will be discussed.

P33.01 Stine  
Daugaard  
Pedersen

INDOOR WORK, ULTRAVIOLET RADIATION, LIGHT EXPOSURE, AND THE RISK OF DEPRESSION AND MULTIPLE SCLEROSIS

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Objectives: The aim of this study is to examine if occupational exposure to UV radiation and light from the sun is associated with diagnosis of depression and multiple sclerosis.

Method: The study population will be a national Danish cohort of all employed workers characterized by annual information on occupation and industry by Statistics Denmark and The Supplementary Pension Fund since 1981. Current and long-term occupational exposure of UV radiation and light will be estimated by a Job Exposure matrix (JEM) providing estimates of the proportion of working hours spent indoor versus outdoor and quantitative annual measures of light and UVR exposure. The exposure estimates will be linked with the study population by industry, occupation, and calendar year. We have collected 7 days illuminance recordings from 576 workers. Along with 500 new recordings, these will be used for the JEM. Incident diagnosis of MS will be obtained from the Danish National Multiple Sclerosis Registry and redemption of prescription of antidepressant medication as proxy of depression will be obtained from The Danish National Prescription Registry.

Results: We hypothesize that recent low exposure to sunlight is associated with an increased risk of antidepressant use and cumulated low exposure to sunlight is associated with an increased risk of multiple sclerosis.

Conclusion: The study will take advantage of objective measurements of sunlight for development of a JEM and registerbased information on outcomes. The results are expected to produce new insight into the association between occupational exposure to sunlight and the risk of

depression and multiple sclerosis.

- P33.02      Sorosh      CARPAL TUNNEL SYNDROME AND CARPAL TUNNEL SYNDROME-LIKE  
Tabatabaeifar      SYMPTOMS IN RELATION TO MECHANICAL EXPOSURES ASSESSED BY A  
JOB EXPOSURE MATRIX: A TRIPLE CASE-REFERENT STUDY
- S. Tabatabaeifar<sup>1</sup>, S.W. Svendsen<sup>2</sup>, B. Johnsen<sup>3</sup>, A. Fuglsang-Frederiksen<sup>3</sup>, P. Frost<sup>1</sup>*
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- Objectives: To evaluate relations between occupational mechanical exposures and (1) carpal tunnel syndrome verified by ENG (ENG+CTS) and (2) CTS-like symptoms with normal ENG (ENG-CTS).
- Methods: We plan a triple-case referent study of 1000 ENG+CTS and 1000 ENG-CTS cases identified at a university department of clinical neurophysiology. For each case, two sex, age, and primary care centre matched controls will be sampled (risk set sampling). Both retrospectively and prospectively identified cases will be included with standardized clinical examination of the last-mentioned group. Conditional logistic regression analyses will be performed comparing the two case control sets, while unconditional logistic regression will be applied comparing ENG+CTS cases to ENG-CTS controls. Questionnaire information will be collected on job history, lifestyle, symptoms, and disability. Job titles will be linked to a job exposure matrix (JEM) based on measurements of hand-wrist movements (goniometer measurements) and expert ratings.
- Results: The main hypothesis is that exposure-response relations will be found for ENG+CTS, but not for ENG-CTS with respect to forceful work and awkward wrist postures, while repetitive work will show exposure-response relations in both groups. The Danish Working Environment Research Fund has granted financial support for a 3-year PhD project starting January 2014.
- Conclusion: The study will take advantage of specific and well documented case diagnoses and independent exposure assessment. The results are expected to produce new insights into exposure-response relations between occupational mechanical exposures and risk of CTS.
- P33.03      Giovanni      NUMBER AND LOCATION OF LESIONS FOR THE OPTIMISATION OF THE  
Ometto      SCREENING INTERVAL IN DIABETIC RETINOPATHY
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A recent study concluded that it is possible to construct a model for optimising the interval between visits during screening for diabetic retinopathy in low-risk patients (Mehlsen et al. 2012). However, the model fails to predict the interval for high risk patients, suggesting that more risk factors should be identified and included. Three groups of visits were selected from the database at Aarhus University Hospital's Department of Ophthalmology from those who had the following interval recommended by both the doctor and the existing model. It was possible to select two groups of visits where the doctor and the model were concordant and one group where they were discordant on either the longest or the shortest interval. Each fundus photograph from the visits was analysed and four types of lesions were recorded. The number and percentage of the lesions and their centre position with regards to the areas defined on a previous study (Hove et al. 2004) were stored in an array of features associated with the relative fundus photograph. Considering the concordance and the discordance on the interval the two possible values of a dependent variable in a classification problem, an extraction of the best isolated features and a 10-fold cross validation were performed to assess their significance. The best isolated features could not help the discrimination of the groups of concordant on the longest interval and discordant. It was concluded that the distribution of diabetic retinopathy lesions has no influence on the model building on cross-sectional data, but may be predictive for future development of vision threatening diabetic retinopathy.

P33.04      Claus Hedebo    ACCELERATED LEARNING IN ANESTHESIOLOGY  
                  Bisgaard

*C.H. Bisgaard*

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Methods: Interventional case-control study.

Intervention group is subjected to deadlines for documented competency in 5 basic anesthesia skills within the first 12 weeks of training. This is in part achieved by increasing mannequin based skills training by the participating departments, prior to the performance of the procedure in patients.

Control group from another region is trained in a more traditional manner, whenever possibility arises, no fixed deadlines. All participants are basic trainees with little or no prior knowledge of the basic skills investigated;

General anesthesia in the expected uncomplicated case. Arterial Canulation. Spinal Anesthesia. Epidural Analgesia. Central Venous Catheter insertion (Ultra Sound Guided).

Data: Data on supervision, competency date and independent production of the key skills on self reported online forms, cross referenced to production databases for the individual departments. Clinical score cards for key procedures in order to evaluate quality of performance of the skills.

#### Hypotheses:

- 1: By systemizing mannequin based skills training trainees will acquire skills faster and enhancing the patient safety in the clinical performance.
- 2: Accelerated training will lead to earlier autonomy of the trainees and to increased autonomous production.
- 3: By systemizing skills training and earlier independent procedural mastery in trainees, specialist time will be freed for more specialist demanding tasks, to greater extent than the time invested in enhanced skills training.
- 4: The "head start" proposed in hypothesis 1 will be maintained throughout the first year of training compared with the control groups.

P33.05      Marie Vad      CAN CHRONIC POSTOPERATIVE PAIN AFTER INGUINAL HERNIA REPAIR BE RELATED TO OCCUPATIONAL MECHANICAL EXPOSURES?

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Background: Approximately 9500 men aged 18-65 years have a primary inguinal hernia repair each year. Chronic postoperative pain (CPP) is considered the most important negative outcome of inguinal hernia repair. We have recently found longer duration of postoperative sickness absence among patients with high occupational mechanical exposures (Vad et al, under review). Maybe this can be explained by exposure-related CPP.

Aim: Our aim is to evaluate the hypothesis that the risk of CPP increases with increasing occupational mechanical exposures in terms of duration of standing/walking and total load lifted per day.

Methods: Six months after a primary inguinal hernia repair, we will send out a postal questionnaire to approximately 6000 men who are active in the labour market. The outcome will be the proportions of these men who report inguinal pain with an intensity >2 on a Numeric Rating Scale. Exposure estimates will be obtained from a Job Exposure Matrix based on expert ratings (Rubak et al 2014). Self reported measures of exposure will also be obtained, but can be vulnerable to recall bias. We will collect questionnaire information on potential risk factors that cannot be obtained from the Danish Hernia Database, including job title, occupational psychosocial factors, body mass index, smoking habits, and sports. Questionnaire information on early postoperative sickness absence will also be collected.

Results and perspectives: We expect that 60% will respond. If occupational mechanical exposures can be identified as risk factors, a transient reduction in workload after inguinal hernia repair might reduce the risk of

CPP.

- P33.06      Dmitri Zintchouk      EFFECT OF GERIATRIC MEDICAL INTERVENTION ON ELDERLY REFERRED FOR REHABILITATION

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Geriatric assessment in hospitalized elderly is shown to increase survival and decrease the number of elderly people admitted to nursing homes or sheltered housing. About 50% of elderly treated at rehabilitation units in Denmark are admitted to nursing homes or specialized senior housing. The aim of the study is to investigate the effect of geriatric medical intervention to frail elderly, 65+ years old, referred to a rehabilitation unit. The effect parameters are: number of contacts to the hospital, general practitioners and home care services, the patients' functional level, quality of life, institutionalization rate, mortality. The predictive factors that characterize elderly who benefit from the intervention will be assessed. The project is an open randomized study with a follow-up period of 3 months. The intervention group: Participants are assigned to an outpatient program in the Department of Geriatrics, assessed by a geriatrician within the first three days of admission to the rehabilitation unit where they receive standard rehabilitation. The control group: Participants receive standard rehabilitation without involvement of the geriatrician. The geriatric medical intervention includes: medical history, medication review, physical examination, paramedical clinical assessment and follow-up (including medication optimization). The hypothesis is that the geriatric medical intervention will do benefit to the frail elderly and reduce hospital contacts by 25%. 185 participants are required in each group to show a significant difference. The project is currently enrolling participants (n=232). Midway interim analysis showed no difference in mortality rate between the groups.

- P33.07      Ditte Lou Langhoff Gantriis      HOME ENVIRONMENT IN FAMILIES WITH PARENTS DIAGNOSED WITH SCHIZOPHRENIA OR BIPOLAR DISORDER: A CROSS-SECTIONAL COHORT STUDY

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**Background:** Inadequate home environment has been reported to increase the risk of developing psychopathology. However, few studies have focused on the home environment among high risk children of parents diagnosed with schizophrenia or bipolar disorder.

**Aim:** The aim is to investigate if there is a correlation between offspring exposure to parental mental illness and level of inadequate home environment as well as level of expressed emotions in the relation between parent and child.

**Method:** This blinded, cross-sectional, cohort study comprises 500 seven-year old children with one, two or none of the parents registered with a diagnosis of schizophrenia or bipolar disorder. The cohort is established using Danish national registers. Parents with schizophrenia or bipolar disorder are matched with healthy controls based on gender of the child and community. Exposure to parental mental illness is quantified as number of months the child has been living with the affected parent. The ongoing data collection commenced in December 2012 and is completed by January 2016. At present, 285 families are included. Level of support and stimulation in the home is assessed with a semi-structured interview called MC-HOME with child and primary caretaker (Middle Childhood-Home Observation for Measurement of the Environment). Level of expressed emotions in the caregiver-child relation is explored from the R-FMSS (Revised-Five Minute Speech Sample).

**Perspective:** Characterization of home environment among children with high familial risk of developing severe mental illness will elucidate which families are in need of support and early intervention.

P33.08      Esben Næser      A POPULATION-BASED STUDY OF PATIENTS WITH NON-SPECIFIC CANCER SYMPTOMS.DIAGNOSTICS AND PROGNOSTICS

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**Background:** More than 25% of all cancer patients present with non-specific cancer symptoms (NSCS). As a consequence, the cancer patient pathway for patients with serious non-specific symptoms and signs of cancer (NSSC-CPP) was introduced in 2011. This group of patients is undescribed in literature and we know little about clinical patient characteristics, diagnosis and prognosis for patients with NSCS.

**Aims:** This study aims 1. to analyse the diagnostic value of blood tests used in cancer diagnostics in the NSCS-CCP, 2. to describe symptoms, clinical findings and diagnoses of patients referred with NSCS to diagnostic centre at Silkeborg Regional Hospital and 3. to analyse the prognosis for patients

referred with NSCS to the diagnostic centre at Silkeborg Regional Hospital.

Methods: Study 1 is a cohort study of patients referred to the NSCS-CCP during a 3-year period. In study 2 and study 3, we use a database to register patients referred for clinical evaluation at the diagnostic centre. Data on diagnosis and death cause are collected from registries.

Analyses: In study 1, we will analyse the results of blood tests in incident cancer patients referred with NSCS. In study 2, we will describe the medical history, clinical findings and diagnosis of patients referred for clinical evaluation at the diagnostic centre. In study 3, we will analyse one-year survival rates and hospitalisation during the first year after referral for patients referred to clinical evaluation at the diagnostic centre.

Perspectives: The current dataset describes a relatively unknown patient population in cancer diagnostics. Knowledge on rational diagnostics of patients with NSCS may lead to optimization of the NSCS urgent referral pathway.

P34.01      Malene Beck      HEADLESS MEALS! OBSERVATIONS OF THE TRADITIONAL MEALTIMES AT THE NEUROLOGY WARD. A PH.D. STUDY IN PROGRESS

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This study aims to improve mealtimes for patients hospitalized following a stroke or other neurological diseases.

A determined effort has been made to optimize the nutrition of hospitalized patients. However, the organization of the mealtimes and the relational and aesthetic aspects have not received similar attention. This means that all other tasks continue with undiminished intensity when patient meals are served and eaten.

This study was based on a qualitative design. Twenty-five observations of the mealtimes were systematically conducted. Data was collected from a Danish department of neurology. The observations varied across time (morning, none and evening), day (holiday, weekend, weekday), staff, and patients. Field notes were taken at the spot and quotes were written directly. After transcription, the text material was analyzed and interpreted using a phenomenological-hermeneutic approach by the philosopher Paul Ricouer.

Three main themes were identified in the analysis: 1) physical space and paraphernalia, 2) aesthetics and atmosphere and 3) rituals and habits. Spaces around the mealtimes were shown to be very atmospheric and informal to patients regarding what they could expect to eat and not at least how they should eat it.

The inclusion of aesthetic elements, familiarity and the tone among staff showed to be important elements for the patient's desire to eat. However, these elements were challenged by the design of the physical space and

the institutional structures, such as time limits for serving the food. In result, the meals could be served as a headless task without recognition of the mealtime being sensed with the patient's whole body and not only by the mouth.

- P34.02      Birthe  
Annemarie  
Thomsen
- NON-ATTENDANCE IN SCREENING FOR CARDIOVASCULAR DISEASES (CVD) AND DIABETES (DM) AMONG DANISH WOMEN
- B.A.D. Thomsen*
- Vascular Research Unit, Viborg Hospital
- Background: Non-attendance in screening offers is a general problem associated with increased morbidity and mortality. Additionally, the (cost-)effectiveness of screening programmes may be influenced by the attendance rates. Exploring non-attendance is part of a PhD project of which the overall objective is to estimate the cost-effectiveness to population-based screening for CVD and DM in Danish women aged 60, 65, 70 and 75.
- Aims: To explore reasons for non-attendance in screening for CVD and DM in Danish women and to explore non-attenders' perception of screening.
- Methods: Exploring non-attendance was based on a hermeneutical approach. A semi-structured interview guide was developed with references to the literature on non-attendance in CVD and DM screening. Face-to-face interviews with 10 non-attenders were conducted in September-October 2013. Reasons for non-attendance were categorized into main themes.
- Results: Three main themes were revealed: 1) finding the screening program personal irrelevant, 2) insufficient knowledge related to diseases, disease prevention and potential benefits of attending and 3) prejudice against the healthcare system and screening in general.
- Conclusion: Non-attendance was found to be associated with previous negative experience with the healthcare system, distrust in healthcare professionals and screening in general. Findings indicated that the decision of non-participation had been made on the basis of insufficient knowledge related to disease prevention, diseases and the purpose of the screening programme. More than half of the non-attenders reported having regretted non-participation or being doubtful about their decision.

- P34.03      Marie  
Mortensen
- CONSTRUCT VALIDITY OF THE PERCEIVED STRESS SCALE AMONG ADULT DANES IN THE CENTRAL DENMARK REGION
- M. Mortensen<sup>1</sup>, E. Ørnbøl<sup>2</sup>, M. Vestergaard<sup>3</sup>, P. Bech<sup>4</sup>, F. Breinholt Larsen<sup>5</sup>, M. Lasgaard<sup>6</sup>, K. Sparle Christensen<sup>1</sup>*

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**Background:** Psychological distress considerably impacts the quality of life worldwide, and stress is a known risk factor for depression and anxiety disorders. The Perceived Stress Scale (PSS) assesses the degree to which respondents see their life as unpredictable, uncontrollable and overloaded. The PSS has previously been studied by methods from classical test theory. We aim to explore the construct validity of the PSS by methods from modern test theory.

**Methods:** The study population consists of 30,000 citizens in the Central Denmark Region, who completed the PSS in the Danish National Health Survey in 2010. We examined if the collected data fitted the Rasch model and studied item ranking, differential item functioning (DIF) for gender and age, local item dependence and unidimensionality as well as ceiling and floor effects in PSS responses.

**Results:** The data did not fit the Rasch model for all ten items and the five response categories. Item 4 had the largest misfit in most performed analyses. Response categories were combined (collapsed) for two of the ten items to improve the model fit. The analysis showed floor effect in the responses and no unidimensionality, but no DIF were found. In addition, local independence was found between some of the items. After several modifications, including merging of response categories and deletion of items, we found that the data still did not fit the Rasch model.

**Perspectives:** Adjustments of the existing PSS scale are required. The results suggest that we currently face scalability challenges with the current Danish version of the PSS scale.

P34.04      Mette Lise  
Lousdal

COUNTY-BASED TRENDS IN BREAST CANCER STAGE DISTRIBUTION IN RELATION TO ORGANIZED SCREENING IN NORWAY: AN OPEN COHORT STUDY

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**Background:** In a previous study, mammography screening increased early-stage breast cancer incidence without subsequent reduction in late-stage. We aim to refine the analysis and account for the gradual introduction by comparing stage-specific incidence during the first round and later rounds with the period before.

**Methods:** An open cohort study covering the county-by-county introduction of organized screening in Norway. Data on stage, age, and county at date of diagnosis were obtained from the Cancer Registry for the period 1987-2011 (42.4m person-years) for all women with first-time breast cancer.

Stage-specific incidence in women aged 50-69 was compared with women aged 20-49 by Poisson regression. For the younger control group "pseudo-introduction" was constructed. Moreover, trends in stage III+ were separately examined in counties with longest follow-up.

Results: The incidence of localized breast cancer among women aged 50-69 doubled during the first round and in later rounds (ratio: 1.94 (95% CI: 1.80; 2.09)) relative to the incidence before. Compared with the slight increase in background incidence in the younger group, the increase in the screened group was 71% (57; 86) higher in the later rounds. The incidence of stage III+ increased slightly in the first round and returned to the previous level in later rounds (1.02 (0.88; 1.18)). Compared with the concurrent increase in the younger group, the increase in the screened group was 12% (-3; 25) lower.

Conclusion: Screening was followed by a considerable increase in early-stage cancers and an insignificant decrease in late-stage cancers. Further analyses should follow birth cohorts to target women that should have benefitted.

P34.05      Sanne Marie Thysen      CHILDHOOD VACCINATIONS AND CHILD SURVIVAL IN GUINEA-BISSAU: A REANALYSIS

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Background: Vaccines are designed to protect against specific diseases and have been tested for this effect rather than their effect on overall mortality. Several studies show that vaccines have a broader effect than what can be explained by the protection against target diseases: Live vaccines (Bacillus Calmette-Guérin (BCG) and measles vaccine (MV)) reduce mortality while the inactivated diphtheria-tetanus-pertussis (DTP) vaccine is associated with increased mortality. In 2014 WHO's Strategic Advisory Group of Experts for the immunisation program recognised the importance of these non-specific effects (NSE) and recommended further research. The datasets which originally showed non-specific effects were analysed in the 90s and the knowledge has greatly expanded since, for example we now know that the sequence of vaccines matter: DTP after MV is associated with increased mortality while MV after DTP reduces mortality.

Methods: In 2000, the Bandim Health Project published a paper describing the mortality of children with and without BCG, DTP and MV based on data collected in rural Guinea-Bissau in 1990-96. We will re-analyse the data from this period using vaccination status assessed at home visits and vital status assessed at the following visit to evaluate the effects of the different vaccination histories on mortality.

Hypotheses: BCG or MV as the most recent vaccine is associated with reduced mortality while DTP is associated with increased mortality. Combined administration of BCG and DTP or MV and DTP is associated with reduced mortality compared with DTP only.

We will evaluate time since vaccination and number of vaccine doses. All



analyses will be stratified by sex.

- P34.06 Tina Wang Vedelø  
OPTIMISATION OF THE INTEGRATED BRAIN CANCER PATHWAY; A STUDY OF PATIENT EXPERIENCES AND NEED FOR INFORMATION, CARE AND SUPPORT  
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Background: Primary Malignant High Grade Glioma (HGG) is a devastating diagnosis and for patients with glioblastoma the median survival is 14,6 months. HGG patients often suffer from both psychical and cognitive symptoms due to the tumor's position in the brain. The shock of the diagnosis, in combination with the multiple symptoms, has shown to affect the patient's abilities to understand information, communicate with health professionals and express needs of care and support. In Denmark, patients go through the "Integrated Brain Cancer Pathway", which leaves a limited amount of time for information. This could explain the unmet information and supportive care needs reported by Danish HGG patients.  
Aim: The aim of this study is to develop knowledge about the "Integrated Brain Cancer Pathway" as experienced by HGG patients. What is most important when receiving the diagnosis of HGG, and which needs do patients have when going through accelerated cancer treatment and care?  
Objectives: 1) To gain an understanding of the patient's life situation and experiences of diagnosis, treatment and care and 2) To identify and describe the supportive care needs and specific information needs of these patients.  
Design: A case study is chosen to provide detailed information of the needs of Danish HGG patients. The researcher follows 3-5 cases from referral and until operation and radiation therapy has been completed.  
Method: Methods to obtain data are observation, conversation, research interview and reading documents. Expected sources of empirical data are patients with HGG, relatives and significant others of HGG patients, health professionals, the patient's general practitioner, patient journals.
- P34.07 Sara Marie Hebsgaard  
FROM BODILY SENSATIONS TO SYMPTOMS OF ILLNESS IN EVERYDAY LIFE  
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Denmark has poor cancer survival compared to similar countries, and one of the reasons is a long patient interval (time from onset of symptoms until healthcare seeking). Existing research on healthcare seeking in relation to

cancer has primarily been conducted retrospectively and with a focus on already diagnosed patients. Often they conclude that late healthcare-seeking is due to problems of symptom awareness and lack of knowledge. These studies, however, rarely consider the question of how symptoms are experienced and interpreted as symptoms in the first place within a particular sociocultural context.

Through perspectives of sensorial anthropology and embodiment theory, this project aims at understanding how bodily sensations are transformed into symptoms in need of medical assessment and how healthcare-seeking practices take form within the context of everyday life. Methodologically, this has been carried out as a prospectively oriented long-term ethnographic fieldwork in a Danish middleclass neighborhood.

People experience bodily sensations on a continuum from something they barely notice to serious acute conditions that need immediate action. What is at play when people sense, interpret and more or less consciously place their sensations within this continuum? This presentation will outline some of the perspectives that appear when looking at symptoms; not as fixed biological entities but rather as continuously negotiated interpretive processes. In particular, we discuss the ways in which current biomedical thinking and practice are embodied in interpretations of sensations into symptoms and in healthcare-seeking practices in everyday life.

P34.08 Michael Schriver

#### DEVELOPMENT OF THE EXPRESS TOOL TO EVALUATE SUPPORT IN EXTERNAL SUPERVISION OF HEALTH CENTERS IN RWANDA

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Sub-Saharan Africa bears 25% of the global burden of disease but have only 1.4% of the physicians and 2.8% of the nursing and midwifery personnel.

In Rwanda, health centers are the backbone of primary health care where nurses diagnose disease and prescribe medicine. They often work in relative isolation with few opportunities for clinical training and professional development.

Supervision of health centers is a potential avenue for strengthening the support of primary care services. In low-income settings such external supervision often differs from clinical supervision by being primarily control or administration oriented. Primary care providers express a need for more clinical training and support in supervision, yet no validated tools were found to evaluate supervision in these contexts.

We developed the ExPRESS tool to measure the degree of training and support in external supervision of primary care facilities from the viewpoint of supervisees. Items were constructed using interviews with providers and supervisors in Rwanda and 18 existing supervision evaluation tools. A simplistic, idiom-free English language was applied to ease cultural adaptation and translation to any African country. The tool was translated

to Kinyarwanda, and content validity was improved and explored through back translations, expert meetings and cognitive testing with supervisors and health providers through in-depth interviews and focus group discussions.

The final 30-item tool will undergo factor analysis and test-retest for reliability. The aim is to develop a tool applicable for supervision monitoring and improvement as well as research.

- P34.09      Nikolaj Raaber    EMERGENCY MEDICAL TECHNICIAN TREAT-AND-LEAVE PATIENTS RECEIVING TELEMEDICINE CONSULTATION WITH EMERGENCY MEDICAL DISPATCH PHYSICIAN - A CONTROLLED BEFORE AND AFTER PILOT-STUDY

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Introduction: Dispatch of an ambulance represents the first step on the path of treatment for acutely ill patients. Changing the course of this path affects all parts of the health care system dealing with emergency patient care.

The objective of this study is to evaluate a systematic telemedical assessment by an Emergency Medical Dispatch Center (EMDC)-physician. In this study, patients who received an ambulance after dialing 1-1-2 but were not critically ill were assessed. We want to examine if the proportion of patients transported to hospital thereby can be reduced, saving costs and time.

Methods: This study is designed as a controlled before and after study: A period of systematic prehospital teleconsultation from ambulances to EMDC physician 24 hours a day every day is compared with a historical period without teleconsultation. In the study period, the Prehospital Emergency Medical Dispatch Center, Aarhus, was manned 24/7 with physicians experienced in emergency care. All non-critically ill patients in the Central Denmark Region who called 1-1-2 and received an ambulance were given a telemedical assessment by the EMDC physician.

Results: Almost 700 contacts between Emergency Medical Technicians (ambulance personnel) and EMDC-physicians were made. Data analysis is in progress.

- P34.10      Lene Odgaard    ACCESS TO HIGHLY SPECIALIZED REHABILITATION FOLLOWING SEVERE  
Hellmund      TRAUMATIC BRAIN INJURY

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**Background and aim:** Patients with highly complex rehabilitation needs after traumatic brain injury (TBI) are referred to highly specialized rehabilitation (HS-rehabilitation). We aimed to identify incidence rates and predictors of HS-rehabilitation among patients surviving severe TBI.

**Patients and methods:** Patients admitted to HS-rehabilitation after surviving severe TBI 2004-2012 were identified from The Danish Head Trauma Database and from The Danish National Patient Registry. Patients not admitted to HS-rehabilitation after surviving severe TBI 2010-2012 were identified from The Danish National Patient Registry. Overall incidence rates of surviving severe TBI and incidence rates of admissions to HS-rehabilitation were estimated and compared. Patient-related predictors of being admitted to HS-rehabilitation among patients surviving severe TBI were identified using multivariable logistic regression.

**Results:** The average incidence rate of surviving severe TBI was 3.3/100,000 person years. Incidence rates of HS-rehabilitation were in general stable around 2.0/100,000 person years. Overall, 84% of all patients surviving severe TBI were admitted to HS-rehabilitation. Male gender, younger age and pre-injury working status were independent predictors of HS-rehabilitation among patients surviving severe TBI.

**Conclusion:** The vast majority of patients surviving severe TBI were admitted to HS-rehabilitation. Our study suggests some inequity in access to HS-rehabilitation despite a health care system based on equal access for all citizens.

P35.01      Annette  
                  Zøylner

PATIENT INVOLVEMENT IN DEVELOPMENT OF DIFFERENTIATED CLINICAL  
PATHWAY PROGRAMMES IN WOMEN WITH BREAST CANCER

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Patient involvement is on the agenda of both professionals and politicians to improve the quality and safety of health care services and to increase patient self-management. In the development of clinical pathway programmes for breast cancer surgery at Aarhus University Hospital (AUH), patients and relatives have so far not been considered a resource in organisational quality improvement. The individual patient is predominantly followed in an outpatient setting; this requires patients and relatives to take on an active role, which is not possible for all patients and relatives. Therefore, there is a need for differentiating pathways to meet the different needs and expectations.

The aim of the project is to develop and evaluate a method to involve patients and relatives directly in the establishment of individualised clinical pathway programmes in breast cancer. Action research is the overall design, implying that action and research are carried out in parallel and that research is conducted in interaction between the study participants and the researcher. Data is generated by means of ethnographic field studies, focus groups, and dialogue meetings. The setting is the Section of Breast and Endocrine Surgery at the Department of Surgery at AUH.

Participants are women operated for breast cancer and their relatives, and health care professionals. The project will generate new knowledge about how patients and relatives can contribute directly to the development of differentiated clinical pathway programmes in breast cancer. The project will also develop and evaluate a method for direct organisational patient involvement, which will presumably be useful in other contexts.

P35.02      Anne Sofie      AN EPIDEMIOLOGICAL INVESTIGATION OF DAIRY PRODUCT INTAKE AND  
                   Dam Laursen      SUBSEQUENT RISK OF STROKE

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Stroke remains a major killer worldwide, which warrants research addressing primary prevention. Even though research regarding dairy product intake and stroke is inconclusive, a diet rich in low-fat dairy products is recommended for stroke prevention. The inconsistent findings may reflect methodological issues in previous studies including lack of classification of stroke into subtypes.

The aim of this project is to clarify the role of dairy product intake in relation to the risk of total stroke and its various subtypes by applying the approaches presented below:

Study 1: A follow-up study investigating whether low-fat dairy product intake compared with whole-fat dairy products is associated with stroke incidence and whether fermented dairy product intake compared with non-fermented dairy product intake is associated with stroke incidence.

Study 2: A follow-up study investigating whether an increased intake of low-fat dairy products and a simultaneous decreased intake of whole-fat dairy over time is associated with stroke incidence.

Study 3: A case-cohort study investigating the association between the milk fatty acids pentadecanoic acid and heptadecanoic acid, measured in adipose tissue, and stroke incidence.

Study 4: A follow-up study investigating how different trajectories of compliance with a diet pattern, characterized by a high intake of low-fat dairy products, fruits, vegetables and a low intake of saturated fat, are associated with stroke.

Ideally the results from this study can be used to update dietary recommendations, food policy and food production initiatives.

P35.03      Tove Lise      HOME-BASED REHABILITATION FOR COMMUNITY DWELLING ELDERLY  
                   Nielsen      CITIZENS - A STUDY OF EFFECT AND CITIZENS' PERSPECTIVES

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The ability to perform daily activities independently may decrease with age, and with the growing proportion of elderly citizens in Denmark, the number in need of municipal home care can be expected to rise. Therefore, various types of home-based rehabilitation are offered, which aim at improving the performance of daily activities through rehabilitative means in the homes of elderly citizens.

The aim of the PhD study is, through a Mixed Methods Design, to:

- 1) Review literature on effect of home-based rehabilitation and on the citizens' perspectives,
- 2) Investigate the effect of an 11-week home-based client-centered and goal-oriented occupational therapy rehabilitation program for elderly citizens, compared to the usual municipal practice, in terms of changes in activity performance and satisfaction, motor and process skills and quality of life,
- 3) Gain insight into elderly citizens' and OT's perspectives on home-based rehabilitation with an emphasis on the citizens' involvement, the influence on everyday life, self-efficacy, and quality of life.

The conclusive thesis may help to inspire future planning and performance of effective and client-centered interventions for elderly citizens.

By November 2014, the literature review is in the initial phase. The intervention and follow-up assessments of the RCT have been performed, and the last data is expected within a month after which the analyses can begin.

- P35.04      Sofie IIsvard      GENERAL PRACTITIONERS' DISCRETIONS IN PREVENTIVE CONTEXTS - A QUALITATIVE INTERVIEW STUDY OF HOW GENERAL PRACTITIONERS' LIFESTYLE SPILL OVER TO THEIR PREVENTIVE STRATEGIES.

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In Denmark, as in other welfare countries, the general practitioner (GP) is the first point of contact in the health services, which stresses the GP's role as gatekeeper and mediator of the health services. The GP's work tasks are characterized by a relatively extensive discretion, especially in opportunistic preventive contexts, in which there are no clear-cut guidelines about when and how to target symptom free citizens' lifestyle to modify their behavior. The empirical question addressed in this article is whether GPs' health perceptions and preventive strategies in general practice reflect a unified professional discretion, or whether their discretion is also influenced by their personal preferences. Based on semi-structured

interviews with 15 general practitioners, we exploratively examine how general practitioners understand health and prevention, and how they talk about their preventive strategies. Despite the GPs' uniform educational background and professional ideology, which might cause them to perceive and address health and prevention in similar ways, our analysis show that the GPs' preventive strategies vary widely. Drawing on Bourdieusian theory, we explain this variation by taking a point of departure in the GPs' own lifestyle preferences and habitual dispositions, which function as a classificatory scheme in exactly the judgment of others' lifestyle. We find a strong pattern of correspondence between the GPs' preventive strategies and their own lifestyle preferences, meaning that GPs act relatively autonomously, and might differently implement preventive initiatives and differently categorize citizens as patients.

P35.05 Maria Wielsøe BREAST CANCER RISK IN THE GREENLANDIC INUIT POPULATION

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Breast cancer (BC) has been increasing worldwide and among females the most frequently diagnosed cancer and the leading cause of cancer death. The incidence of BC has previously been low among the Inuit, but since the 1970's a considerable increase has been observed in the Arctic including Greenland. The risk of BC is thought to be modified by lifestyle and exposure to environmental contaminants. Given the increase in BC incidence, one would expect the etiology to be related to exposures that also have increased over time such as environmental persistent organic pollutants (POPs) including perfluorinated alkylated substances (PFAS).

The Arctic populations have some of the highest known body burdens of legacy POPs being potential endocrine disrupters interfering with the oestrogen- (ER), androgen- (AR), aryl hydrocarbon (AhR) receptor, thyroid hormone (TH) function and steroid enzymes such as aromatase.

The hypothesis of the PhD project is that changes to a more westernized lifestyle in combination with high serum levels of environmental contaminants, certain genetic polymorphisms, and changed microRNA expression are factors contributing to the increase in BC risk in Greenlandic Inuit women.

The study includes 31 cases and 115 matched controls enrolled in 2000-2003 and approximately 50 cases and 50 matched controls enrolled in 2011-2014. The samples from 2000-2003 have been analysed and showed that high serum levels of PFAS and changes in reproductive life were risk factors. The samples from 2011-2014 will be analysed during this PhD project, including new analyses and follow-up on the trends.

P35.06 Cecilie Nørby A QUALITATIVE STUDY OF ILLNESS MANAGEMENT OF HIGHLY EDUCATED PEOPLE WITH A DEPRESSION, THEIR COLLEAGUES AND EMPLOYERS IN

Thisted

## ORDER TO STRENGTHEN THE DEVELOPMENT OF RETURN-TO-WORK STRATEGIES

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Introduction: Depression is the leading cause of disability globally. In Denmark 3.3% of the adult population suffers from major depression, and approximately 61% never consults a doctor. Scientific evidence shows that the workplace has an effect on the individual's illness experience, illness management and treatment process. Level of education and stigma also has an influence.

There is a lack of knowledge on how highly educated people with a depression manage their illness, in relation to the workplace. There is a need for this type of knowledge in order to develop targeted return-to-work strategies.

Aims: 1. To evaluate knowledge about experience and management of depression from the perspective of respectively the individual, colleagues and employers, including differences related to socioeconomic status. 2. To investigate illness experience and illness management of highly educated people with a depression, in relation to the workplace. 3. To investigate how colleagues experience and manage co-workers with a depression. 4. To investigate how employers experience and manage employees with a depression.

Material and method: Data is generated through a systematic review, individual interviews with highly educated people and employers as well as focus group interviews with colleagues. Deductive content analysis is used to analyse the qualitative data. The deductive application of categories and codes will be based on ICF.

Perspective: The project contributes with knowledge on people with a higher education in order to strengthen the development of effective and targeted return-to-work strategies. The knowledge is also expected to be applicable to lower education groups.

P35.07      Line Hvidberg      BARRIERS TO HEALTHCARE SEEKING, BELIEFS ABOUT CANCER AND THE ROLE OF SOCIO-ECONOMIC POSITION. A DANISH POPULATION-BASED STUDY

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Background: Cancer-related health behaviours may be affected by barriers to healthcare seeking and beliefs about cancer. The aim was to assess anticipated barriers to healthcare seeking and beliefs about cancer in a sample of the Danish population and to assess the association with



socio-economic position.

Methods: A population-based telephone interview with 3,000 randomly sampled persons aged 30 years or older was performed using the Awareness and Beliefs about Cancer measure from 31 May to 4 July 2011. The Awareness and Beliefs about Cancer measure includes statements about four anticipated barriers to healthcare seeking and three positively and three negatively framed beliefs about cancer. For all persons, register-based information on socio-economic position was obtained through Statistics Denmark.

Results: Two anticipated barriers, worry about what the doctor might find and worry about wasting the doctor's time, were present among 27% and 15% of the respondents, respectively. Overall, a high proportion of respondents concurred with positive beliefs about cancer; fewer concurred with negative beliefs. Having a low educational level and a low household income were strongly associated with having negative beliefs about cancer.

Conclusion: The fact that worry about what the doctor might find and worry about wasting the doctor's time were commonly reported barriers call for initiatives in general practice. The association between low educational level and low household income and negative beliefs about cancer might to some degree explain the negative socio-economic gradient in cancer outcome.

P35.08      Jörg  
Schullehner      DRINKING WATER N-POLLUTION AND PUBLIC HEALTH EFFECTS: NITRATE EXPOSURE OF THE DANISH POPULATION DURING THE LAST 35 YEARS

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In Denmark, drinking water supply is highly decentralized and fully relying on simple treated groundwater. At the same time, Denmark has an intensive agriculture, making groundwater resources prone to pollution with nitrate. Drinking water quality data covering the entire country for over 35 years are registered in the publicly-accessible database JUPITER. These data were analysed to determine the fraction of population exposed to elevated nitrate concentrations. Data from 2,852 water supply areas in the 98 Danish municipalities were for the first time digitalized, collected in one dataset and connected to the JUPITER database. Public water supplies are extensively registered; private wells supplying only few households are neither monitored nor registered sufficiently. The study showed that 5.1% of the Danish population was exposed to nitrate concentrations > 25 mg/L in 2012. Private well users were far more prone to exposure to elevated nitrate concentrations than consumers connected to public supplies. While the fraction exposed to elevated nitrate concentrations amongst public supply users has been decreasing since the 1970s, it has been increasing amongst private well users, leading to the hypothesis that the decrease in nitrate concentrations in drinking water is mainly due to structural changes

and not improvement of the groundwater quality as such. A combination of this new drinking water quality map with extensive Danish health registers will permit an epidemiological study on health effects of nitrate, namely gastrointestinal cancers, as long as the lack of data on private well users is addressed. This will be the focus of the remaining part of this PhD project.

P36.01      Louise Holm Schæbel      THE INFLUENCE OF TRADITIONAL INUIT DIET, VITAMIN D AND PERSISTENT ORGANIC POLLUTANTS ON INFLAMMATION

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Background: Chronic low-grade inflammation is involved in the initiation and progression of atherosclerosis and ischemic heart disease. This was rare in pre-western Inuit who lived on a diet that consisted mainly of marine mammals rich in n-3 fatty acids.

Objectives: To assess the association between biomarkers of inflammation and the intake of traditional Inuit diet, vitamin D and Persistent Organic Pollutants (POPs).

Methods: YKL-40 and hsCRP, as well as plasma 25-hydroxy-vitamin D, were measured in serum from 535 Inuit and non-Inuit living in Nuuk in West Greenland or in rural East Greenland. POPs will be measured at Centre de toxicologie du Québec / INSPQ, Canada. Dietary habits were assessed by an interview-based food frequency questionnaire.

Results: YKL-40 was significantly higher in Inuit than in non-Inuit, in Inuit with a higher intake of traditional Inuit diet, and in Inuit from rural compared to urban areas. Inuit had significantly higher hsCRP compared to non-Inuit and hsCRP increased in parallel with intake of traditional Inuit foods. Alcohol associated with a decrease in hsCRP in Inuit. YKL-40 and hsCRP increased with higher intakes of traditional Inuit diet after adjusting for ethnicity, gender, age, smoking, alcohol intake and BMI. Data concerning the association between vitamin D and inflammation are not ready for statistical analysis.

Conclusions: Biomarkers of inflammation vary in parallel with the intake of traditional Inuit diet. A diet based on marine mammals from the Arctic does not reduce inflammatory activity. The association between two components in the traditional Inuit diet, vitamin and POPs, and inflammation will be objects for future analysis.

P36.02      Belle Mia Loft      DEVELOPMENT OF A NURSING INTERVENTION TO OPTIMIZE REHABILITATION FOR HOSPITALIZED PATIENTS WITH STROKE; A PH.D. STUDY IN PROGRESS

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**Aim:** To develop, test and evaluate the feasibility of a nursing intervention to optimize the rehabilitation of patients hospitalized after stroke. The project is guided by the British Medical Research Council framework for development of complex interventions. This abstract is presenting the first part of the initial phase where the aim is:

To identify and define the need for training/progress in the selected clinical practice, as well as getting knowledge of the selected practice, in terms of barriers and facilitators of significance for the development and testing of the intervention.

**Method:** The study takes place on a stroke unit in a University Hospital in the the Capital Region of Denmark. As part of the pre-clinical phase, the clinical practice was uncovered through observational studies and interviews. The observation studies were carried out over a period of 30 days. Selected situations where patients and nursing staff interact form the basis for the focused observations. Afterwards 10 patients and 12 health professionals from the care staff were interviewed using a semi-structured interview guide. The American ethnographer Spradley's method provides the methodological approach. Data will be analyzed using qualitative content analysis inspired by Graneheim and Lundman.

**Results:** The study is ongoing, but we expect to gain knowledge of how caregivers integrate rehabilitation initiatives and goals planned together with the patient in the planning and performance of care, which factors promote/inhibit integrative nursing, which situations have particular potential for integrating nursing, and where the greatest need is for optimizing integrative nursing.

P36.03      Liv Solvår  
Nymark

#### ECONOMIC EVALUATION OF ALTERNATIVE MEASLES-MUMPS-RUBELLA VACCINATION SCHEDULES IN DANISH CHILDREN

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**Background:** The public health benefits of providing routine measles-mumps-rubella (MMR) vaccination against the targeted diseases are well-documented. Several studies suggest that there may be beneficial effects of the live measles vaccine beyond the protection against the targeted disease; i.e. non-specific effects (NSE). Randomised trials in West Africa suggest that early receipt of measles vaccine reduces the risk of hospital admissions for non-measles-related infections. A register study including >500 000 Danish children indicates that the MMR vaccine reduces the risk of any infectious-disease related hospital admission by 14%.

Aims: To consider the added value of NSE in cost-effectiveness evaluations of childhood vaccination programmes.

Methods: A decision analytic model is proposed to estimate and compare the averted numbers of any infectious disease admissions and associated costs for four different MMR vaccination schedules:

A: One dose of MMR delivered at 15 months of age and a second dose at 4 years-old-age which reflects the current recommended schedule in Denmark.

B: One dose of MMR delivered at 13 months of age.

C: Two doses of MMR delivered at 6 months and 15 months of age.

D: Two doses of MMR delivered at 6 months and 13 months of age.

The decision analytic model utilises a range of coverage rates, the risk of being hospitalised for any infectious disease-related admission and associated cost variables. A Markov model is also introduced to account for benefits that do not accrue immediately, may attenuate over time and the timing of avoided future infections.

P36.04      Stefan  
Nygaard  
Hansen

#### EXPLAINING THE INCREASE IN AUTISM PREVALENCE: THE PROPORTION ATTRIBUTABLE TO CHANGES IN REPORTING PRACTICES

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Introduction: The prevalence of autism spectrum disorders (ASDs) has increased markedly in recent decades, which has been suggested could be caused in part by changes in reporting practices. Danish health registries have undergone two major changes in reporting practices; the diagnostic criteria used for assigning diagnoses were changed in 1994 and the registries began to include outpatient diagnoses in 1995.

Aim: To quantify the degree to which changes in reporting practices can explain the increase in ASD prevalence.

Methods: All children born alive in the period 1980-1991 were followed until ASD diagnosis, death, emigration, or end of follow-up on December 31, 2011, whichever occurred first. The two changes in reporting practices in 1994 and 1995 were modelled as time-dependent covariates in a stratified Cox regression model while adjusting for calendar time trends. Based on the estimated hazard ratios, we calculated the proportion of the observed prevalence increase that can be directly attributed to the two changes in reporting practices.

Results: The change in diagnostic criteria was associated with a hazard ratio of 1.42 (0.99-2.04), while the inclusion of outpatient diagnoses was

associated with a hazard ratio of 1.62 (1.24-2.12). We estimated that 33% (0%-70%) and 42% (14%-69%) of the increase in observed ASD prevalence can be explained by the change in diagnostic criteria and the inclusion of outpatients, respectively. Together, the two changes can explain 60% (33%-87%) of the increase in observed ASD prevalence.

Conclusion: Changes in reporting practices can account for most (60%) of the increase in the observed ASD prevalence in children born 1980-1991.

- P36.05      Berit Skjødeberg Toftegaard      THE EFFECT OF CONTINUING MEDICAL EDUCATION (CME) ON GENERAL PRACTITIONER'S KNOWLEDGE AND ATTITUDE

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Background: Danish cancer patients are generally diagnosed and treated at more advanced disease stages compared to other Nordic countries. This has called for a focus on earlier diagnosis meaning earlier referral for investigation. Selecting patients for referral for suspected cancer is a complex procedure, which is influenced by the general practitioner's (GP's) knowledge, skills, clinical judgement, risk-taking disposition and attitude. Therefore, the GP's ability to assess the risk of cancer and the GP's threshold for referral are two critical elements in the diagnostic process. Nevertheless, we do not know whether continuing medical education (CME) can influence the GP's knowledge and attitudes towards cancer diagnosis.

Aim: The aim was to evaluate the effect of an CME in early cancer diagnosis on GP knowledge and attitude.

Methods: We invited all 831 GPs from the Central Denmark Region to participate in the CME, which was a multifaceted three-hour course in early cancer diagnosis. One month before and seven months after the CME, all GPs were asked to complete questionnaires on their current knowledge and attitude.

Results: In total, 202 GPs (24.3%) completed the questionnaire before and after the CME; 81 of these GPs participated in the CME. Preliminary results of a paired before-after study of responses will be presented.

Perspectives: The achieved knowledge will contribute to the understanding of whether and how general practitioners' diagnostic skills in relation to cancer may be improved.

- P36.06      Anne Mette Falstie-Jensen      FULL COMPLIANCE WITH HOSPITAL ACCREDITATION WAS ASSOCIATED WITH LOWER 30-DAY MORTALITY RISK

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Objective: To examine the association between compliance with hospital accreditation and 30-day mortality.

Method: A nationwide population-based follow-up study covering admissions at all public, non-psychiatric Danish hospitals accredited by the first version of The Danish Healthcare Quality Programme (DDKM). Inpatients diagnosed with one of 80 primary diagnoses were included with their first admission at either fully accredited (n=76 518) or partially accredited hospitals (n=200 462). A follow-up activity was requested for partially accredited hospital either by submitting additional documentation (n=96 785) or having a return visit (n=103 677).

Main outcome measures: 30-day mortality after admission. Multivariable logistic regression computed odds ratios (OR) for 30-day mortality risk according to level of accreditation adjusted for six potential confounding factors and for a possible cluster effect at hospital level.

Results: 30-day mortality risk for inpatients at fully and partially accredited hospitals was 4.14% (95% CI: 4.00-4.28) and 4.28% (95% CI: 4.20-4.37), respectively. Inpatients at fully accredited hospitals had a lower risk of dying within 30 days after admission compared with inpatients at partially accredited hospitals (adjusted OR of 0.83; 95% CI: 0.72-0.96). A reduced risk of 30-day mortality was shown for inpatients at hospitals required to submit additional documentation compared with having a return visit (adjusted OR of 0.83; 95%CI: 0.67-1.02).

Conclusion: Admissions at fully accredited hospitals were associated with a lower 30-day mortality risk than admissions at partially accredited hospitals.

P36.07      Susanne Friis      DOCUMENTATIONS OF NURSING ACTIVITIES AND PATIENT SAFETY IN THE  
                 Søndergård      OPERATION ROOM - THE SIGNIFICANCE OF A STUDY VISIT

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Introduction: This study concerns issues which implicate the documentation of nursing activities in the operating room (OR). The study is testing whether the use of a documentation tool strictly related to the nursing activities in the OR can improve patient safety. Among other evidenced-based documentation tools, a tool developed by the Association of periOperative Registered Nurses (AORN) was selected. AORN has developed this IT-based tool "Perioperative Nursing Dataset Syntegrity Framework" (PNDS) toward documentation of evidence-based nursing activities in the OR.

Aim: The aim for this part was to gather knowledge of the background, development and use of the tool, and to establish cooperation with the Association of periOperative Registered Nurses.

Methods: In order to gather information from the PNDS, a study visit in the

US was planned. An agreement on an eight-week stay was made with the AORN. Participation with the PNDS Syntegrity Framework Team in order to gather the theoretical perspective was scheduled. Furthermore, site visits to different hospitals were also scheduled. The hospitals were all included because of their exemplary use of PNDS.

Results: The site visits and the face-to-face work with the team during the eight weeks have resulted in high insight into the development and use of the PNDS and in a cooperation agreement with AORN. Furthermore, cooperation was established with the software company with which the Danish version of PNDS will be developed.

P36.08      Lotte Maxild      N-3 AND N-6 PUFAS; INTERACTIONS, GENETIC PATHWAYS AND RISK OF  
Mortensen      ATRIAL FIBRILLATION

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The aim of this study is to investigate the relation between dietary intake of polyunsaturated fatty acids (PUFAs), genotype of genes involved in the metabolism of the PUFAs and risk of atrial fibrillation (AF).

AF has been associated with inflammation in several studies. The PUFAs, consisting of two subgroups, the n-3 and the n-6 fatty acids, affect the inflammatory system in being precursors to the eicosanoids, a group of metabolites that affect physiologically important processes, including the inflammatory system. The inflammatory effects of the two PUFA-subgroups differ, with the eicosanoids from the n-3 being less inflammatory than those synthesised from n-6. The PUFAs are transformed in the PUFA pathway in which the two subgroups are metabolized by the same enzymes in a competitive way.

Hypotheses:

1) There is a biological interaction between intake levels of n-3 and n-6.

2) Polymorphisms in the genes of the PUFA pathway affect the risk of AF through differential processing of n-3 and n-6 resulting in genetic predisposition towards light or strong inflammatory phenotypes.

Approach: I will use data from the Diet, Cancer, and Health Cohort comprising genetic material and diet information from 57,000 participants. Since enrolment 3,400 have developed AF. The plan is to analyse the intake of PUFAs and SNP-polymorphisms in the selected candidate genes and correlate this with diagnosis of AF.

The studies in this PhD program include:

- 1) Primary exposures (intake of n-3, n-6 and SNPs) and biological interaction and risk of AF analysed with epidemiological methods
- 2) Advanced modeling using bioinformatics aiming at analyzing the interaction of the multiple factors involved.

P37.01	Rasmus Offersen	<p>A NOVEL TLR9-AGONIST (MGN1703) INCREASES NK-CELL ACTIVATION AND KILLING OF HIV-INFECTED CELLS</p> <p><i>R. Offersen, M. Tolstrup, T.H. Mogensen, L. Østergaard, O. Søgaard</i></p> <p>Department of Infectious Diseases, Aarhus University Hospital, Skejby</p> <p>Introduction: In the search for a cure against HIV, recent clinical trials have demonstrated proof that latent HIV can be disrupted safely in patients on antiretroviral treatment, by histone de-acetylase inhibitors. However, reactivation of latently infected cells alone does not reduce the HIV reservoir - probably due to insufficient immune-mediated killing of reactivated cells.</p> <p>MGN1703 (dSLIM) is a novel immunomodulatory compound agonizing TLR9. In an ex vivo setup, we wanted to test the capability of MGN1703 to activate natural killer (NK) cells in order to enhance immune-mediated killing of HIV-infected cells.</p> <p>Methods: Peripheral blood mononuclear cells from HIV-infected donors were stimulated with MGN1703, LPS, or media as reference. Using flow cytometry, cells were analyzed for activation markers (CD69), degranulatory capacity was assessed by expression of CD107a and intracellular IFN-<math>\gamma</math>, when co-cultured with K562 cells. Further, purified NK-cells were tested in a viral inhibition assay.</p> <p>Results: MGN1703 induced a five-fold increase in NK-cell activation, but also CD4, CD8 and NKT-like cells were activated. Further, NK-cells stimulated with MGN1703 exhibited stronger degranulatory capacity (CD107a) and IFN-<math>\gamma</math> production, and ultimately they displayed superior killing of HIV-infected autologous CD4 T cells.</p> <p>Conclusion: MGN1703 is a novel TLR9-agonist ready for clinical use. Ex vivo testing on immune cells from HIV-patients shows a remarkable increased NK-cell activation and killing of HIV-infected cells. These encouraging data support clinical testing of MGN1703, with main focus of safety and immunomodulatory capability.</p>
P37.02	Flemming Kromann Nielsen	<p>MEASUREMENT OF BONE MARROW LESIONS BY MR IMAGING IN KNEE OSTEOARTHRITIS: THE SENSITIVITY TO CHANGE ASSESSED BY TWO QUANTITATIVE METHODS</p> <p><i>F.K. Nielsen, N. Egdal, D.A. Peters, A.G. Jurik</i></p> <p>Department of Clinical Medicine, Aarhus University Hospital</p>



Purpose: To compare two quantitative methods of measuring BMLs in knee osteoarthritis (KOA); one with computer assisted automatic segmentation (CAS) and one with manual segmentation (MS).

Methods and materials: Twenty-two persons with primary medial KOA obtained MRI at baseline and follow-up (median 11 months in between).

Two readers assessed the sagittal STIR sequences of the 44 examinations independently. Mean values and standard deviations of the signal intensity (SI) of the normal marrow in the lateral condyles were obtained and used for defining the threshold values. Volumes of bone marrow in the medial femoral and tibial condyle with SIs exceeding the threshold values (BML) were measured.

Sensitivity to change (STC) was calculated by comparing BML-involvement at baseline between the two readers using a Bland-Altman analysis. Any change in BML-volume exceeding the 95% limits of agreement was considered significant.

Results: Threshold values of CAS and MS were almost identical. The median/relative BML-volume in the femur was 1319 mm<sup>3</sup>/10% and 1828 mm<sup>3</sup>/15%, in the tibia 941 mm<sup>3</sup>/7% and 2097 mm<sup>3</sup>/19% using CAS and MS, respectively. The two methods were thus not comparable; the CAS method recorded the volume of voxels exceeding the threshold values whereas manual segmentation included varying voxels, some with normal SI. The inter-observer agreement was best by CAS with bias values of -0.1-0.01% BML compared with 0.26-0.36% by MS. The STC was best using CAS. A significant change of BML by CAS was outside the limits of -2.0%-4.7%, by MS -6.5%-8.2%.

Conclusion: CAS was superior to MS in detecting changes over time. The BML-volumes measured by the two methods were not comparable.

P37.03      Stig Hill  
                 Christiansen

#### EFFECTS OF ANTIMICROBIAL PEPTIDES ON HUMAN LEUKOCYTES

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Chronic inflammatory disorders often cause an aberrant destruction of healthy body tissue. Multiple sclerosis (MS), Systemic Lupus Erythematosus (SLE) and psoriasis are important examples of these conditions with a high prevalence in Western countries.

In virtually any organism, immunity to infections is contributed by evolutionary conserved peptides with a striking ability to eradicate microbial organisms, hence, named antimicrobial peptides (AMPs). AMPs are secreted as inactive precursors and proteolytically activated into potent antimicrobial peptides. The current dogma is that AMPs act to destabilize the cell membrane of microorganisms through electrostatic interactions between the cationic AMPs and the anionic microbial membrane. The electrostatic interactions allow these peptides to permeabilize the membrane lipid bilayer, thereby leading to membrane

destabilization.

An emerging literature now suggests that AMPs exhibit a number of immunomodulatory properties. In this respect, a predominant focus has been on the augmentation of the leukocyte response to infection. Nevertheless, apart from exhibiting direct antimicrobial effects, AMPs have been demonstrated in several pathophysiological conditions, such as in chronic inflammatory disorders.

While AMPs are actively explored as a new class of anti-microbial agents, the possibility that AMPs additionally possess an effect on mammalian leukocytes has not been extensively studied. In the present study, we investigate the influence of AMPs on human leukocytes.

P37.04      Kristina      MOXIFLOXACIN PHARMACOKINETIC PROFILE AND EFFICACY  
Margareta      EVALUATION IN THE EMPIRIC TREATMENT OF COMMUNITY-ACQUIRED  
Öbrink-Hansen PNEUMONIA

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When antimicrobials are used empirically, pathogen minimal inhibitory concentration (MIC) equal to clinical breakpoints or epidemiological cut-off values must be considered. This is to ensure that the most resistant pathogen subpopulation is appropriately targeted to prevent emergence of resistance. We determined the pharmacokinetic profile of moxifloxacin 400 mg/day in 18 patients treated empirically for community-acquired pneumonia (CAP). We developed a population pharmacokinetic model to assess potential efficacy of the drug and to simulate the maximal MICs allowed to obtain recommended pharmacokinetic-pharmacodynamic (PK-PD) estimates. Moxifloxacin plasma concentrations were determined the day after therapy initiation using high performance liquid chromatography. Peak drug concentrations ( $C_{max}$ ) and 24-hour area under the free drug concentration-time curve values ( $fAUC_{0-24}$ ) predicted for each patient were evaluated against epidemiological cut-off MIC values for *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Legionella pneumophila*. PK-PD targets adopted were  $C_{max}/MIC \geq 12.2$  for all pathogens,  $fAUC_{0-24}/MIC > 34$  for *S. pneumoniae* and  $fAUC_{0-24}/MIC > 75$  for *H. influenzae* and *L. pneumophila*. Individual predicted estimates for  $C_{max}/MIC$  and  $fAUC_{0-24}/MIC$  as well as simulated maximal MICs, resulting in target attainment for oral and infusion administration of the drug, were suitable for *S. pneumoniae* and *H. influenzae*, but not for *L. pneumophila*. This study reveals key information relevant to the empirical treatment of CAP while highlighting the robust and flexible nature of this population PK model to predict therapeutic success.

P37.05 Kasper Lisager Jønsson HISTONE DEACETYLASE INHIBITORS PROTECTS CD4+T-CELLS FROM HIV-1 INFECTION.

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Histone deacetylase inhibitors (HDACi) are known anticancer drugs<sup>1</sup>. Studies have shown that HDACi features anti-inflammatory properties and certain HDACi can reactivate latent reservoirs of HIV in CD4+T cells<sup>2,3</sup>. Nevertheless, the bioactivity of HDACi treatment of uninfected cells in conjunction to HIV-1 infection has not been investigated.

In this study, we characterized the role of two potent preclinical HDACi's (romidepsin and panobinostat) on HIV-1 infection of CD4+T-cells and macrophages. We proved that priming of CD4+T cells with HDACi significantly reduced HIV infectivity and replication. In contrary, HDACi priming of primary human macrophages showed no protection. Protection in CD4+ T cells was not correlated to increased cell death due to HDACi treatment. In a viral outgrowth assay, generally used to determine the potency of HDACi to reactivate reservoirs in HIV patients, HDACi treatment protected cells from re-infection, thus decreasing the assay sensitivity. To address the protective role of HDACi, we screened the gene regulation of 42 different antiviral factors in CD4+T cells. The multiplex Fluidigm qPCR method found that, of 42 antiviral genes, a majority was down-regulated by HDACi treatment 8 hours post treatment, with the exception of the antiviral restriction factor IFIT1 and ISG15.

This study is the first in the world, which has shown that HDACi exerts a protective role during infection with HIV-1 in CD4+T cells. Besides being able to reactivate latent reservoirs of HIV in patients, HDACi may also protect uninfected cells, which strengthens the safety issue of using HDACi in the clinic.

Reference:

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P37.06 Anne Margrethe Trolborg PLASMA LEVELS OF PATTERN RECOGNITION MOLECULES OF THE LECTIN PATHWAY ARE ALTERED IN SLE PATIENTS - A PILOT STUDY

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Background/purpose: Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease where the Complement System plays a key

pathogenic role. The study objective was to measure levels of the pattern recognition molecules of the Lectin Pathway: mannan binding lectin (MBL), collectin-L1 (CL-L1), and the three ficolins in plasma of patients with SLE and compare with age and gender matched healthy controls. Further, we analyzed for correlation between the plasma levels and characteristic SLE manifestations.

Methods: Plasma was obtained from a cross-sectional cohort of 58 SLE patients. We collected prospectively demographic and clinical data. For comparison, blood samples were collected from 65 age and gender matched healthy blood donors. Using time resolved immuno-fluorometric assays developed at our own lab, plasma levels of MBL, CL-L1, M-ficolin and H-ficolin were measured. L-ficolin was measured by ELISA.

Results: Mean plasma levels of CL-L1 and M-ficolin were significantly lower and H-ficolin significantly higher in patients with SLE compared to healthy controls ( $p < 0.0001$ ). A statistically significant difference between plasma levels of H-ficolin in SLE patients with lymphopenia compared to the non-lymphopenic patients was found ( $p = 0.0434$ ).

Conclusion: Plasma concentrations of several of the pattern recognition molecules of the Lectin Pathway were significantly altered in a cross-sectional cohort of SLE-patients showing low levels of CL-L1 and M-ficolin and high levels of H-ficolin. Lymphopenia in patients was associated with a high level of H-ficolin. The association with a key element of the clinical picture, lymphopenia, may indicate a pathogenic role of Ficolin-3 in SLE.

P37.07 Sara Bisgaard Jensen ENDOGENOUS RETROVIRUSES IN MULTIPLE SCLEROSIS: NEW DEVELOPMENTS

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The etiology of multiple sclerosis (MS) is unknown and treatment limited to symptomatic treatment. Both genetic and functional studies link human endogenous retroviruses (HERVs) to the autoimmune disorder. Interestingly, epidemiological studies show that the incidence of MS among HAART treated HIV-patients is lower than expected. HERVs originate from prehistoric germ line infections by exogenous retroviruses resulting in the integration of the provirus within the host genome. During their chromosomal residence, most HERVs have accumulated post-insertional mutations rendering them dysfunctional. Several attempts have been made to reconstruct a putative ancestor of the HERV-K family. The aim of this project is to study the effect of anti-HIV treatment on the expression capacity of a reconstituted so-called oricoHERV-K system in which reversion of post-insertional mutations and codon optimization facilitates production of HERV-K type virus-like particles (VLPs).

Retroviral VLPs will be generated by coexpression of the pcDNAoricoHERV-K113\_GagProPol and pcDNAoricoEnv-V5 plasmids in HEK293T cells. This

procedure is known to produce mature VLPs with protease activity. Moreover, the supernatant of the VLP producing cells displays reverse transcriptase (RT) activity. In our study, the anti-HIV drug panel will include inhibitors of the retrovirus-specific enzymes i.e. RT, integrase, and protease inhibitors. The effect will be validated by the Cavid RT-assay, PCRs, WB, and virus titer assays.

We expect the anti-HIV drugs to have a restrictive effect on oricoHERV-K expression; lowering RT activity and thereby suggesting that antiretroviral drugs are valid candidates for MS therapy.

P37.08      Sofie Eg  
Jørgensen      MDA5 MUTATION IMPAIRS INFLAMMATORY AND ANTIVIRAL RESPONSES IN A PATIENT WITH ECTODERMAL DYSPLASIA WITH IMMUNODEFICIENCY

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Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) is a disorder characterised by osteopetrosis, lymphedema and, as the name implies, ectodermal dysplasia. EDA-ID patients are also affected by a combined immunodeficiency with reduced inflammatory responses and hypogammaglobulinemia. This immunodeficiency results from mutations in either Nuclear factor- $\kappa$ B (NF- $\kappa$ B) essential modulator (NEMO) or I $\kappa$ Ba. Mutations in NEMO and I $\kappa$ Ba lead to reduced NF- $\kappa$ B activation and thereby decreased inflammatory and antiviral responses to pathogens, which increases susceptibility to pathogenic bacteria, mycobacteria, fungi and viruses in patients with EDA-ID.

A 9-year-old boy with EDA-ID was examined for mutations in NEMO and I $\kappa$ Ba, but none could be identified. Whole exome sequencing was therefore performed and a rare heterozygous loss-of-function mutation was identified in the RIG-like receptor (RLR) Melanoma differentiation-associated factor (MDA)5 gene, which encodes a cytosolic RNA sensor that induces interferon (IFN) and anti-inflammatory cytokines upon activation.

The identified mutation introduces an amino acid substitution, Asn160Asp, in the CARD domain of MDA5. The immunological consequences of the mutation are being investigated by quantitative RT-PCR, western blotting, and luciferase reporter assays. The mutant MDA5 protein has so far been found unable to induce activation of NF $\kappa$ B and TLR dependent induction of various cytokines and IFN are impaired. Furthermore, no MDA5 protein expression can be detected in PBMCs from the patient.

P38.01      Jesper Weile      INITIAL PATIENT EVALUATION IN THE EMERGENCY DEPARTMENT WITH POINT-OF-CARE ULTRASONOGRAPHY.

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Background: Timely and accurate diagnostics in the Emergency Department (ED) can shorten length of stay, decrease morbidity and mortality and prevent adverse effects of incorrect treatment. Ultrasonography is a non-invasive diagnostic tool. Diagnostic point-of-care (POC) ultrasonography has been widely used since the late 1950's with no proven adverse effects like radiation from traditional X-ray or computer tomography. POC ultrasonography can be performed by emergency physicians during initial work-up with adequate accuracy. A series of studies have shown an increase in diagnostic accuracy from 21% to 30 % and changes in patient management from 19% to 41% of cases after focused POC ultrasonography. These studies underline the significance of POC ultrasonography in the ED.

Previous studies have examined selected groups of patients. Furthermore, the studies have been designed for specific evaluations such as the heart or the lungs. The findings by ultrasonography examination on patients outside these selected groups are unclear. The total potential impact of using POC ultrasonography on unselected patients has not yet been clarified.

Methods: The study is a prospective descriptive observational study. 406 unselected random patients in a rural emergency department are included. A structured point of care ultrasonographical examination is performed on all patients. The treating physician is interviewed on the influence of the ultrasonographical exam on the diagnostics and treatment of the patients.

Endpoints: All findings are described. All changes in diagnostics and/or treatment will be described. No results are yet ready for publication as the data acquisition is ongoing.

P38.02      Kaja Zuwala      MACROMOLECULAR PRODRUGS OF AZT AND RBV - TOWARDS A TREATMENT FOR INFECTION WITH HIV AND HCV

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Macromolecular prodrugs based on polymers improve solubility of the drugs and increase circulation time, reduce both immunogenicity and toxicity, and give many opportunities for targeted delivery and combination therapy. Some formulations of therapeutics conjugated to polymers have been accepted by the Federal Drug Administration, and many are being investigated in clinical trials. The achievements in the field

of clinical use of macromolecular prodrugs (MP) can be applied in treatment of viral diseases which pose great healthcare and economic burden. Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) together infect nearly 200 mln people worldwide and are responsible for severe debilitating diseases. Here we present two new approaches in the design of antiviral therapeutics. First one is based on ribavirin (RBV) which has been long used in a treatment of viral hepatitis. Anemia, the main side effect of RBV caused by accumulation of the drug in erythrocytes, can be overcome by conjugating RBV to the polymer. We prove that such MP of RBV has anti-HIV activity and is less toxic at therapeutical concentration. In the second approach, we employed self-immolative linker in conjugating anti-HIV drug azidothymidine (AZT) to the polymer. The linkage was stable in PBS and FBS and released the drug only inside the cell.

P38.03      Lars Skov  
Dalgaard      RISK AND PROGNOSIS OF BACTERAEMIA AMONG PATIENTS ON CHRONIC PERITONEAL DIALYSIS: A POPULATION-BASED COHORT STUDY

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Background: Invasive bacterial infections are common among patients on chronic peritoneal dialysis (PD). This population-based cohort study aims to estimate risk and mortality of bacteraemia among PD patients.

Methods: End-stage renal disease patients in Central and North Jutland who initiated PD during 1995-2010 were identified (PD patients). For each PD patient, up to 10 persons from the general population matched on age, gender, and municipality were sampled. Regional microbiology databases provided information on bacteraemia. PD patients and their matched population controls were observed from the date of PD initiation until the first episode of bacteraemia, emigration, death, or end of PD, whichever came first. Bacteraemia incidence rates (IRs) were computed. Risk factors for bacteraemia were assessed by Cox regression. Kaplan-Meier analysis was used to determine case fatality.

Results: We included 1,025 PD patients and 10,225 population controls providing 1,578 and 62,605 person-years of follow-up (PYFU), respectively. IRs of bacteraemia were 6.08 (95% confidence interval (CI), 4.98-7.43) per 100 PYFU in PD patients and 0.49 (95% CI, 0.44-0.55) per 100 PYFU in population controls. In PD patients, the most common causative microorganisms were *Staphylococcus aureus* (13.5%), coagulase-negative staphylococci (18.8%) and *Escherichia coli* (14.6%). Thirty-day case fatality following bacteraemia was similar among PD patients and population controls, 19% (95% CI, 12%-28%) vs. 20% (95% CI, 17%-24%), respectively.

Conclusions: Bacteraemia constitute a major clinical concern in PD patients. Studies on prevention of PD-related infections should therefore

also consider bacteraemia.

- P38.04      Claus Sixtus  
                  Jensen      EARLY WARNING SYSTEM ON EVOLVING CRITICAL ILLNESS AND  
INTERVENTION IN HOSPITALISED CHILDREN; A REGIONAL MULTICENTRE  
STUDY ON IMPLEMENTATION OF A PAEDIATRIC EARLY WARNING SYSTEM

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Background: Critical illness in the patient and death can potentially be predicted and prevented. Deterioration of the clinical condition of hospitalised patients is often preceded by physiological changes up to 24 hours before death. Despite this several reports show that lack of identification and proper actions in patients developing acute and critical illness remains a problem.

Aim: The purpose of this study is to investigate if Paediatric Early Warning System (PEWS) optimises identification of acute and critically ill children and prevents life-threatening situations.

Design: This PhD study is a multi-centre study designed within a Complex Intervention framework; the study sheds light on the problem, validation of the data collection instrument, testing of the intervention and evaluation. The PhD study involves all paediatric departments and some acute departments in the Central Denmark Region. The project both includes quantitative studies and a qualitative evaluation study.

The studies will have different designs:

Registry study, Validation study, Randomised controlled (RC) intervention study and Evaluation study using focus group interview.

Development and implementation of PEWS is expected to contribute to reduce the number of children developing acute critical illness, number of admissions to intensive care. PEWS is also expected to contribute to increase professional skills and competences in health professionals. Last, but not least, it must be expected that a PEWS model will contribute to reducing the costs for society as an intensive care hospital bed is more expensive than a hospital bed at a general paediatric department.

- P38.05      Steffen Leth      MEMORY CD4+ T CELL SUBSETS IN HIV LATENCY

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Background: Latent HIV infection in memory CD4+ T cells is established when replication competent HIV-DNA integrates into the cellular genome as cells revert to a resting memory state. Global cellular quiescence in the resting memory state also inhibits viral transcription, thus creating state of HIV latency in long-lived immune cells capable of resuming replication upon subsequent reactivation. Reactivation of these latent viral genomes is a therapeutic strategy to eliminate latently infected cells in chronic HIV infection given that latently infected resting memory CD4+ T cells are the primary barrier to HIV eradication. Breaching this barrier requires a comprehensive understanding of the dynamics of longitudinal viral persistence and the susceptibilities of persistent virus to HIV eradication interventions within memory CD4+ T cell subsets.

Objective and methods: Using state-of-the-art cell sorting and digital droplet PCR techniques to characterize the differential contribution and longitudinal variation in measures of viral persistence (e.g. integrated HIV DNA and cell-associated unspliced HIV RNA) within memory CD4+ T cell subsets:

- During long-term virological suppression by highly active antiretroviral therapy.
- Before, during and after therapeutic interventions aimed at inducing HIV expression in latently infected cells.

Hypotheses: We hypothesize that cell-based measures of viral persistence will display differential magnitude and dynamics within memory CD4+ T cell subsets and that therapeutic interventions to induce HIV expression in latently infected cells will have differential effects within memory CD4+ T cell subsets.

P38.06      Uffe Nygaard      EVALUATING SEROLOGICAL BIOMARKERS IN ATOPIC DERMATITIS

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Background: Atopic Dermatitis (AD) is very common in affluent countries with 15-20% of children and 3-4% of adults being affected. Cytokines play a central role in AD as they drive the inflammatory response, reduce the skin barrier function and increase the level of pruritus. It is debated whether biomarkers can help establish an early diagnosis and help monitor treatment response and disease activity. Both TSLP and IL-31 have been proposed as potential biomarkers in patients with atopic dermatitis (AD). However, their clinical applicability in affected children and adults has rarely been studied.

Objectives: To quantify serological levels of TSLP and IL-31 in children and

adults with AD and correlate this to a clinical severity score.

Methods: We included 61 children and 71 adults with verified AD and 31 healthy controls with no history of AD or other inflammatory disease. Severity of AD was assessed according to the SCORing Atopic Dermatitis (SCORAD) index. Serum levels of TSLP and IL-31 were measured by ELISA.

Results: Levels of TSLP were significantly increased in the AD group vs. controls ( $p=0,003$ ) and furthermore between the subgroups AD Children vs. controls ( $p=0,016$ ) and AD Adults vs. controls ( $p=0,002$ ). Levels of IL-31 were significantly increased in the AD group vs. controls ( $p=0,010$ ) and between AD Children vs. controls ( $p<0,001$ ) but not when comparing AD Adults vs. controls ( $p=0,23$ ). Serum levels of neither TSLP nor IL-31 correlated significantly with SCORAD index.

Conclusions: TSLP and IL-31 are valid biomarkers when used as paraclinical evidence of AD, although we find no indication that they can be used in correlation with disease activity.

P38.07 Xianwei Zhang THE PRO- AND ANTI-INFLAMMATORY ROLES OF INTEGRIN CD11B/D18: A TARGET FOR TREATMENT OF THE CHRONIC INFLAMMATORY DISORDERS?

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Integrin  $\alpha_M\beta_2$ , also named Mac-1, CD11b/CD18 or complement receptor (CR) 3, is a member of the  $\beta_2$  integrin family. It is essential for pathogen and denatured protein recognition by myeloid leukocytes such as macrophages. Binding of  $\alpha_M\beta_2$  to its ligands will trigger actin remodeling, which controls the formation of filopodia and phagocytosis by phagocytes. Ligand binding can also lead to degranulation and changes in cytokine expression.

In a previous study, two mutants of C3d (R1254A and D1247E) were proved to be of either reduced (R1254A) or almost negligible (D1247E) binding affinity to CR3. However, the isothermal titration calorimetry (ITC) data left us with the concern that interactions with no heat release or absorption may give false negative results. We would also like to study the binding behavior not only at the isolated protein-protein level, but also at the cellular level.

We have completed experiments based on Surface Plasmon Resonance (SPR) and real-time cellular assays (RTCA). SPR study showed consistent results with ITC, but with more details concerning binding kinetics showing that there might be several binding types of different  $K_D$  and  $k_{off}$  value ranges. RTCA experiments were done with electronic cell-substrate impedance sensing (ECIS). Although results are of similar trend to ITC and SPR, cellular assay showed that the binding impaired mutant (D1247E) is in fact of signal on a quite similar level to the reduced binding mutant (R1254A). These paved the road to further signaling and transcriptome study in our future plan, which will give a better answer to how integrin

$\alpha_M\beta_2$  carries out its diverse functions.

- P38.08      Chenglong Sun      MARCH8 AS A POTENTIAL E3 LIGASE TARGETING ON HSV-1 CAPSID
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- In the infected cells, herpesvirus DNA can be exposed to the cytoplasm, and consequently will be detected as a pathogen-associated molecular pattern (PAMP) by intracellular germline-encoded pattern recognition receptors (PRRs) and induce IFN responses. About 10 intracellular DNA sensors have been identified at this stage. However, knowledge on how viral capsid is detected and targeted for degradation is still unclear. To address this question, we hypothesize that there are E3 ubiquitin ligases which can detect the invading herpesvirus capsid, and catalyze ubiquitination and subsequent proteasomal degradation, which leads to release of genome DNA into cytoplasm. In serial RNAi screens, we identified the E3 ubiquitin ligase membrane-associated RING-CH (MARCH8) as a potential candidate to target HSV-1 capsid for ubiquitination and degradation. Knockdown of MARCH8 in HeLa cells promotes HSV-1 replication. While in macrophage-like THP1-derived MARCH8 KD cell lines stably transfected with MARCH8 shRNA, type 1 IFN induction by HSV-1 is much impaired comparing to in Ctrl-shRNA cell line. Otherwise, confocal imaging data suggest that invading capsid of HSV-1 can co-localize with MARCH8, K48-linked polyubiquitin chains, and proteasomes in THP1 cells. All data now indicate that MARCH8 probably act as an E3 ubiquitin ligase targeting HSV-1 capsid to degradation. We are currently constructing MARCH8 KO cell line by CRISPR, and over-expression system is under planning. These tools will be used to confirm our findings in MARCH8 KD cell lines based on shRNA, and to characterize the process of ubiquitination and degradation of HSV-1 capsid in more details.
- P38.09      Sigrún Alba Jóhannesdóttir      HERPES ZOSTER DIAGNOSED IN THE HOSPITAL SETTING IN DENMARK: INCIDENCE, PATIENT CHARACTERISTICS, AND SUBSEQUENT MORTALITY
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- Background: Accurate estimates for the pre-vaccination burden of herpes zoster in Denmark are lacking, which precludes formulation of evidence-based national guidelines for the zoster vaccine. We examined zoster diagnosed in the hospital setting in Denmark with regard to incidence,

patient characteristics and subsequent mortality.

**Methods:** We identified first-time inpatient, ambulatory, and emergency room zoster diagnoses in the National Patient Registry, 1994-2012. We computed the annual rate (standardized to the 2000 Danish population), the length of stay, the frequency of complications and patient characteristics, and the all-cause mortality.

**Results:** The annual rate was 13.2/100,000 without substantial secular or seasonal trends. Women had higher incidence and median age at diagnosis (13.7/100,000; 71 years) than men (12.6/100,000; 65 years). Incidence increased with age from 3.5/100,000 in 0-19 year-olds to 83.1/100,000 in ≥80 year-olds. Zoster was the primary discharge diagnosis in 71.8% and 70.5% had uncomplicated disease. According to the Charlson Comorbidity Index, 44.9% had none, 17.2% had moderate, 17.3% had severe, and 20.6% had very severe comorbidity. Median length of stay for inpatient primary diagnoses was 4 days (interquartile range: 1-8). The mortality risk was 12.7% for 1 year, 24.3% for >1-5 years, 25.4% for >5-10 years, and 51.0% for 0-10 years of follow-up. Diagnosis in early calendar periods, male sex, increasing age, and high comorbidity burden were associated with increased mortality rates.

**Conclusions:** In Denmark, hospital-diagnosed zoster is most frequent among women and elderly. Patients are characterized by high comorbidity burden and mortality.

P38.10     Dorte Tranberg Hansen     CELLULAR LOCALIZATION OF HERV-ENCODED PROTEINS: VISUALIZATION AND MOLECULAR CLONING

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**Background:** Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system. The cause remains unknown, but human endogenous retroviruses (HERVs) are increasingly in focus as possible participants in the pathogenesis of the disease.

Retroviral envelope (Env) proteins, encoded by HERVs, are expressed in increased amounts on mononuclear cells (particularly B cells and monocytes) from patients with MS. Furthermore, the amount of anti-HERV antibodies in serum and cerebrospinal fluid from patients with MS is increased when compared with healthy controls.

**Aim:** The visualization of expressed HERV Env on mononuclear cells, and the construction of recombinant HERV-H/F Env proteins for expression in mammalian cells.

**Methods:** Using confocal microscopy (Zeiss LSM710), surface expression of HERV-H/F Env epitopes is examined on long-term growing B-lymphoblastoid cell cultures and isolated mononuclear cells obtained from

patients with MS, as well as target cells for transfection. For cloning, PCR with specific primer sets is used to synthesize DNA fragments corresponding to HERV-H/F Env variants for subsequent transformation.

Results and conclusion: HERV-H/F Env was highly expressed on the surface of the MS cell cultures, while no expression was found on the cell lines that will be used for transfection. HERV-H/F Env constructs are in the process of being confirmed and will be used for transient and stable transfection of mammalian cell lines. The pathogenic effect on construct-expressing cells will be assessed by fusiogenic and apoptotic analysis.

Perspectives: Results will contribute new knowledge of the possible involvement of HERVs in MS pathogenesis.

CH.01      Line Flytkjær  
Jensen      HEALTH-RELATED QUALITY OF LIFE, PERCEIVED STRESS, AND NON-  
PARTICIPATION IN BREAST CANCER SCREENING: A DANISH COHORT  
STUDY

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Purpose: Population-based cancer screening is offered in many countries to detect early stages of cancer and to reduce mortality. The efficiency depends on high participation, but many programmes are challenged by a group of non-participants. We investigated associations between health-related quality of life, perceived stress, and subsequent non-participation in breast-cancer screening.

Methods: This population-based cohort study included 4,512 women in the Central Denmark Region who had participated in a Health Survey in 2006 and who were also in the target group for the first public breast cancer screening programme in the same region in 2008-2009. Data on perceived stress and health-related quality of life were collected from the regional Health Survey, while data on screening participation were obtained from a regional administrative register.

Results: A U-shaped association was observed for the physical health status as women with the highest and the lowest physical health scores were less likely to participate in the screening than women with physical health scores in the middle-range category. Women with the lowest mental health scores and the highest perceived stress scores were less likely to participate than women with scores in the middle-range categories.

Conclusions: Women with highest and lowest self-assessed physical health and women with lowest mental health and highest perceived stress were significantly associated with non-participation in breast cancer screening two years later. Targeting these groups in special interventions may be considered to promote equal participation in future breast cancer screening programmes.

CH.02      Rakeł Fuglsang VLDL1 AND VLDL2 KINETICS IN RELATION TO TYPE 2 DIABETES AND  
Johansen      INSULIN RESISTANCE

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Diabetic dyslipidemia is an important cardiovascular risk factor in type 2 diabetes. It is believed that overproduction of larger VLDL1 particles drives the lipid alterations seen in diabetic dyslipidemia, while smaller VLDL2 particles are unaltered. The aim of this study was to compare VLDL1 and VLDL2 kinetics in type 2 diabetic men and nondiabetic subjects.

Twelve type 2 diabetic and 12 healthy men, matched for BMI and age, were recruited. During a study day consisting of a 4-hour basal and a 3 ½ hyperinsulinemic period, primed-constant infusion of ex-vivo labelled [1-<sup>14</sup>C]triolein and [9,10-<sup>3</sup>H]triolein was administered to calculate VLDL1 and VLDL2 steady state kinetics by use of isotope dilution technique.

VLDL1-TG and VLDL2-TG secretion rates were similar in the diabetic and healthy men during the basal and hyperinsulinemic period and suppressed significantly and similarly during hyperinsulinemia. The suppression in VLDL1-TG secretion was, however, greater in healthy men (p=0.04). VLDL1-TG clearance rates were comparable between groups and not altered by hyperinsulinemia. VLDL1-TG oxidation rate was similar in the basal state, but suppressed significantly more during the clamp in healthy compared with diabetic men (p=0.04). GIR were significantly inversely correlated with VLDL1- and VLDL2-TG concentration and secretion rate in the hyperinsulinemic period.

For the first time, VLDL1 and VLDL2 kinetics has been measured by use of an isotope dilution technique. It was found that insulin plays a major role in the down regulation of VLDL1 and VLDL2, and levels are, therefore, increased in insulin resistance likely contributing to diabetic dyslipidemia.

CH.03      Mads Skipper      WHAT LINKS THE HOSPITAL WORK ORGANIZATION WITH  
POSTGRADUATE WORKPLACE LEARNING? A QUALITATIVE CASE STUDY  
OF THREE PAEDIATRIC DEPARTMENTS IN DENMARK

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Background: Several qualitative studies have examined how doctors learn in the workplace. But work is needed to explain how the doctor's learning environment is influenced by the daily work routine and the clinical workplace organization (e.g. team organization, hospital work organization).

Methods: This qualitative study consisted of short time ethnographic

observational case studies in three paediatric departments in Denmark, triangulated with focus-group interviews with key informants; consultants responsible for postgraduate medical education and residents (in paediatrics and family medicine). The methodology and methods were guided by a grounded theory approach. Data was coded through an iterative process followed by inductive thematic analysis.

Results: Data showed that learning something valuable requires an organization of the daily work around four principles. First, junior and senior doctors working together around patient care. Second, a systematic approach with principles of adult learning. Third, committed time between novice and expert. Fourth, considering situational influences (e.g. patient complexity and competence level of junior doctors). Two factors hindering workplace learning were: lack of role models to learn from and too high workload. These negative factors might lead to reduced learning opportunities, less time for reflection and lower quality of supervision and feedback.

Conclusions: This qualitative case study emphasises the importance of knowledge about the organizational culture and structure around post-graduate education, and how this knowledge might facilitate more time for training and reflection, mutual engagement, and shared purpose.

CH.04      Katherina Farr    PERFUSION SPECT USED TO MEASURE PULMONARY FUNCTION BEFORE AND AFTER CURATIVE RADIOTHERAPY IN PATIENTS WITH NON-SMALL-CELL LUNG CANCER

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Introduction: The purpose of the study was to evaluate changes in perfusion on single-photon emission computed tomography (SPECT) as a method of lung function assessment before and after radiotherapy for non-small-cell lung cancer (NSCLC).

Materials and methods: Patients undergoing chemo-radiotherapy for NSCLC were included prospectively. SPECT and global pulmonary function tests (PFT) were performed at baseline, 1 and 3 months after radiotherapy. Functional activity on SPECT was measured by a semiquantitative score. The largest localised defect score (DS) was assessed in each lung by its size, while remaining lung was assessed according to the degree of perfusion heterogeneity. Clinical end-point was radiation pneumonitis graded by CTCAE v 4.

Results: Data on 28 patients were available for preliminary analysis at baseline, 23 patients at 1-month follow-up and 12 patients at 3-month follow-up. DS increased (lung function worsened) significantly at 1 month and 3 months after radiotherapy ( $p=0.02$ ). Results for the first 28 patients showed strong correlation between DS and PFT at baseline with high DS associated with lower PFTs. While DS for remaining lung and total lung at 3 months was significantly correlated with the grade of radiation

pneumonitis, this relationship for PFT was not found. Patients with severe radiation pneumonitis had significantly higher total lung DS ( $p=0.02$ ) and remaining lung DS ( $p=0.04$ ) measured at baseline. PFT were not statistically different in these patients. The study is ongoing and further analysis is underway.

Conclusions: Perfusion SPECT is a valuable method to assess lung function damage after curative radiotherapy and predict pulmonary symptoms.

## CH.05 Kasper Hansen CT, PET AND MRI IN EXPERIMENTAL BAROMETRIC PHYSIOLOGY

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Introduction: Divers are exposed to extreme changes in pressure. During decompression nucleation of inert gas bubbles from supersaturated tissues may lead to decompression sickness (DCS), a potentially disabling or life-threatening situation. Many underlying physiological phenomena attributed to DCS are currently unknown, possibly because it is intrinsically difficult to study model animals during the actual pressurisation and decompression event. We have developed a novel pressure chamber system compatible with CT, PET and MRI scanners, which are capable of non-invasive visualisation of morphology and physiological processes.

Method: First, modality-appropriate phantoms were examined with CT, PET and MRI during pressurisation up to 10 ata (90 meters of water). Secondly, 15 anaesthetised rats (6 control, 9 pressurised) rats were MRI scanned before, during pressurisation to 7 ata for 45 min, and repeatedly during 240 minutes after a decompression rate of 0.5 ata/min. Concurrently, ultrasound was performed of the pulmonary artery in order to record gas bubbles; a traditional marker for DCS severity.

Results: The acquired image signal from pressurised CT and PET phantoms were unchanged, but pressure per se had a significant but weak negative effect on the longitudinal ( $r_1$ ) and transverse ( $r_2$ ) relativity of degassed MRI phantoms. The simulated pressure chamber dive induced significant changes in basic MRI-parameters measured in rat brain.

Conclusion: We have demonstrated a system capable of performing non-invasive in vivo measurements on a rodent model during pressurisation; a very promising application for basic research in barometric physiology and medicine.

## CH.06 Nis Pedersen Jørgensen MBEC MEASUREMENTS MORE ACCURATELY PREDICT TREATMENT OUTCOME THAN MIC IN MURINE MODEL OF IMPLANT ASSOCIATED OSTEOMYELITIS

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We investigated the ability of a MBEC assay to predict treatment outcome of antimicrobial therapy in a murine model of implant associated osteomyelitis caused by *S. aureus* biofilm formation.

Methods: MBEC measurement: Modified Calgary Biofilm Device to assess MBEC of Vancomycin, Linezolid, Daptomycin, Dicloxacillin, Rifampicin and Tigecyclin against *S. aureus* ATCC 12600. MIC was measured with E-test. We used a murine model to investigate the efficiency of Van, Dap, Lin, Dic, Tig) and Rif as either monotherapy or combination therapy. C57Bl/6 mice received a tibia implant colonized with *Staphylococcus*. Treatment was initiated after 11 days and continued for 14 days.

Results: MIC values: Van 2 µg/ml, Lin 1 µg/ml and Dap 0.38 µg/ml. MBEC values: Van >2048 µg/ml, Lin >1024 µg/ml and Dap > 1024 µg/ml. For the selected antibiotics, Van+Rif, Dap+Rif and Lin+Rif all resulted in a reduction of bacterial load of infected tibias compared to control animals of between 1.9 - and 2.5 log CFU (Dap+Rif:  $1.97 \pm 0.26$ , Lin+Rif:  $2.25 \pm 0.16$ , Van+rif:  $2.41 \pm 0.27$ ,  $p < 0.001$ , Figure 1A). Furthermore, the addition of Rif to all three drugs significantly improved antimicrobial activity, as measured by CFU reduction ( $p > 0.005$  for all three drugs). 14 days of antibiotic treatment was without effect on the bacterial biofilm on the surface of the implant, as the different antibiotic combinations failed to reduce the bacterial load.

Conclusion: This study demonstrates that MBEC measurements are better suited than MIC measurement to predict treatment outcome in biofilm associated infections. In addition, the study underlines the difficulties associated with treating mature biofilm infections.

CH.07 Stine Hald

A DIET RICH IN ARABINOXYLAN AND RESISTANT STARCH INCREASES COLONIC BUTYRATE CONCENTRATION AND OCCLUDIN EXPRESSION IN SUBJECTS WITH METABOLIC SYNDROME

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Background: The metabolic syndrome (MetS) is associated with a decreased intestinal defense barrier leading to low-grade inflammation and endotoxemia. The defense barrier consists of epithelial tight junctions including occludin and mucins (primarily MUC2). In in vitro models and animal studies, butyrate modulates occludin and MUC2 expression. We hypothesized that a diet rich in arabinoxylan (AX) and resistant starch (RS) would improve colonic health by increasing the colonic butyrate production and the expression of occludin and MUC2 in subject with MetS.

Methods: Nineteen subjects with MetS completed a 4-week, randomized crossover study with two diet interventions; a healthy carbohydrate diet

(HCD) rich in AX and RS, and a low-fiber western style diet (WSD).

Before and after each intervention endoscopy with tissue samples was done, and stool samples were collected. Colonic MUC2 and occludin expression were analyzed by quantitative RT-PCR, while gas-liquid chromatography was used to detect fecal butyrate concentration.

Results: After HCD fecal butyrate concentration was increased ( $p < 0.01$ ), and the colonic expression of occludin was 1.15 ( $p = 0.005$ ) and MUC2 was 1.20 ( $p = 0.07$ ) fold higher compared to WSD.

Conclusion: Consumption of a 4-week diet rich in AX and RS increased colonic occludin expression and tended to enhance MUC2 expression suggesting an enhanced colonic defense barrier in subjects with MetS.

CH.08      Torbjørn  
              Brøgger

#### THE SURROUNDING TISSUE MODIFIES THE PLACENTAL STEM VILLOUS VASCULAR RESPONSES

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Background: The placenta is the base for the exchange of nutrients, oxygen and waste products for the fetus. The placental vessels hold a crucial role in regulation of blood flow, and compromised function may lead to complications like growth retardation and preeclampsia where no specific treatment is available. In-depth understanding of the mechanisms involved in control of the placental vascular tone is needed to develop new tissue targets for therapeutic intervention. The hypothesis is that the surrounding tissue modifies the vascular responses to different agonists.

Method: From fresh-born placentas, segments of stem villous arteries were carefully dissected. The artery branches were divided. The surrounding tissue was removed from one end and left intact in the other, and the segment was divided to give two ring preparations, with or without tissue. The preparations were mounted in wire myographs and responses to vasoactive agents were compared.

Results:  $pD_2$  values for  $PGF_{2\alpha}$ , Tx-analog U46619, 5-HT and endothelin-1 were significantly lower in preparations with intact surrounding tissue compared to preparations where it had been removed. Moreover, maximal force development ( $E_{max}$ ) was lower in arteries with intact trophoblast after stimulation with high extracellular  $[K^+]$ ,  $PGF_{2\alpha}$  or endothelin-1. These differences partly disappeared in the presence of L-NAME, while indomethacin had no effects.

Conclusion: The perivascular tissue significantly reduces sensitivity and force development of stem villous arteries, partly due to release of NO. This represents a new mechanism for control of human stem villous artery tone.

CH.09      Nikolaj Rittig      ANABOLIC EFFECTS OF AMINO ACID SUPPLEMENTATION DURING ACUTE INFLAMMATION: A HUMAN RANDOMIZED CROSSOVER TRIAL

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Background: Inflammation is catabolic and causes muscle loss. It is unknown if amino acid supplementation reverses these effects during the acute phase of inflammation.

Objective: To test whether amino acid supplementation counteracts endotoxin induced catabolism.

Design: Eight young, healthy, and lean males were investigated three times: (i) normal conditions (Placebo), (ii) endotoxaemia (LPS), and (iii) endotoxaemia with amino acid supplementation (LPS+A). Protein kinetics were determined using phenylalanine, tyrosine, and urea tracers. Each study day consisted of a four-hour basal period and a two-hour hyperinsulinemic euglycaemic clamp period. Muscle biopsies were collected once each period.

Results: LPS administration caused a significant degree of inflammation. Whole body phenylalanine breakdown was elevated during LPS compared to Placebo and LPS+A ( $p < 0.05$ ). Whole body phenylalanine synthesis was higher during LPS+A compared to both Placebo and LPS ( $p < 0.003$ ), and furthermore synthesis was higher during LPS compared to Placebo ( $p < 0.02$ ). Net muscle phenylalanine release was markedly decreased during LPS+A ( $p < 0.004$ ), even though muscle protein synthesis and breakdown rates did not differ significantly between interventions. LPS+A increased phosphorylated mTOR levels ( $p < 0.05$ ) and decreased levels of non-p-4BP1 ( $p = 0.007$ ) without affecting other components of the insulin-signaling cascade.

Conclusions: Amino acid supplementation in the acute phase of inflammation counteracts whole body and muscle protein loss and this is associated with activation of mTOR and the downstream target 4BP1, suggesting a potentially wide therapeutic role for amino acids in inflammatory states.

CH.10      Zahra Nochi      APPROACHES TO DECIPHERING THE BALANCE BETWEEN SURVIVAL AND DEATH MECHANISM IN CELLS WITH MITOCHONDRIAL DYSFUNCTION

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Background and objective: Short-chain acyl-CoA dehydrogenase (SCAD) deficiency is a fatty acid oxidation disorder. Since it is important to delineate if individuals carrying SCAD (ACADS) gene variations are at risk

of developing disease during acute stress, we hypothesized that starvation and/ or fever in symptomatic patients may shift the homeostatic balance towards cell death and treatment by N-acetylcysteine (NAC) can prevent this.

Material and methods: Fibroblasts from a selected SCAD deficient patient and a control were cultured for 0, 6, 12, 24, and 48 hours at normal and stressed conditions. We determined the expression rate of oxidative stress markers (SOD2 and TRAP1) at protein level and measured superoxide generated in the mitochondria using MitoSOX assay.

Results: SOD2 and TRAP1 expressions and also MitoSOX assay showed SCAD deficient cells responded significantly to the stress exposure after 12 hours. The procedure is repeated at 12 hours with 3 of each SCAD deficient, MCAD (Medium-chain acyl-CoA dehydrogenase) deficient and control cells while they are also treated with NAC.

Conclusion: SOD2 and TRAP1 upregulation in SCAD and MCAD deficient cells significantly concludes more oxidative stress, but less damage in MCAD deficient cells than SCAD. NAC, inducer of survival mechanisms, increases SOD2 and TRAP1 expression more in MCAD than in SCAD deficient cells.

CH.11 Anna Budtz-Lilly

# BODILY DISTRESS SYNDROME: PATIENT CHARACTERISTICS AND FREQUENCY IN PRIMARY CARE

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Objective: Bodily distress syndrome (BDS) is a newly proposed diagnosis of functional disorders which is based on empirical research. The objective of this study was to estimate the frequency and describe the characteristics of patients with BDS in primary care.

Method: The study was conducted as a cross-sectional study of primary care patients in the Central Denmark Region. Data were obtained from one-page forms completed by general practitioners, patient questionnaires and national registers.

Results: Of the 1,356 included primary care patients, 230 patients (17.0%, 95% confidence interval (CI), 15.0-19.1) fulfilled the BDS criteria. BDS was associated with middle age, i.e. 41-65 years old (odds ratio (OR) 2.0, 95% CI, 1.3-3.0) and as frequent among men as among women (female sex; OR 0.9, 95% CI, 0.6-1.3). BDS was associated with poor self-assessed health according to the 12-item Short Form Health Survey (SF-12), i.e. physical component summary score < 40 (OR 20.5, 95% CI, 12.9-32.4) and mental component summary score < 40 (OR 3.5, 95% CI, 2.2-5.6). Furthermore, BDS patients were more likely to have high scores on the Symptom Check List for anxiety (OR 2.2, 95% CI, 1.4-3.4) and depression (OR 5.1, 95% CI, 3.3-

7.9). However, mental comorbidity did not account for the poor self-assessed health of BDS patients.

Conclusion: BDS is common in primary care populations and associated with mental health problems and poor quality of life. Hence, there seems to be a considerable need for prevention and treatment of patients with BDS.

CH.12      Randi  
Heidemann  
Gottfredsen

## EXPRESSION AND RELOCATION OF EC-SOD IN NEUTROPHILS

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At inflammatory conditions, neutrophils play a central role in generating reactive oxygen species and proteases to combat invading microorganisms as well as producing a range of cytokines that further mature the inflammatory response. The antioxidant protein extracellular superoxide dismutase (EC-SOD) is the only extracellular protein with the capacity to remove interstitial superoxide. Studies have shown that EC-SOD is associated with both macrophages and neutrophils and that the protein has the capacity to modulate the inflammatory response. We have recently shown that activation of macrophages stimulates the release of EC-SOD into the extracellular space. To further characterize the role of EC-SOD in inflammation, we have analyzed the expression and distribution of the protein in isolated neutrophils. Analyses by flow cytometry and electron microscopy show that EC-SOD is present on the cell surface as well as in intracellular compartments. This observation was further corroborated by sub-cellular fractionation. Interestingly, we show that the protein is redistributed upon cellular activation induced by phorbol myristate acetate (PMA). In line with our results obtained from bone marrow-derived macrophages, we show that the protein is undetectable in the supernatant of resting neutrophils whereas PMA-induced activation relocates the protein to the extracellular space. Moreover, we provide evidence for the association between neutrophil extracellular traps (NETs) and EC-SOD. In concert, our data indicate that activated neutrophils may provide EC-SOD to the site of inflammation, suggesting an active role of the protein in establishing an adequate inflammatory response.

CH.13      Veerle  
Paternoster

## REDUCED BRD1 LEVEL IN MOUSE BRAIN AFFECTS THE EXPRESSION OF PROTEINS INVOLVED IN NEURONAL DEVELOPMENT, MORPHOLOGY AND FUNCTION

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Accumulating data from genetic, cell and animal studies form strong evidence that the Bromodomain-containing 1 (BRD1) gene is involved in the pathogenesis of schizophrenia (SZ) and bipolar disorder (BD). It has been shown that BRD1 interacts with histone modifying enzymes. These protein complexes bind predominantly to transcription start sites of genes which are enriched for schizophrenia risk-genes. Brd1<sup>+/-</sup> mice show schizophrenia-like and reversible depression-like phenotypes. Neurons of Brd1<sup>+/-</sup> mice show less branching and lower spine density.

We aim to analyze overall quantitative changes in the frontal cortex, hippocampus and striatum proteomes of female Brd1<sup>+/-</sup> mouse. Both total protein extracts as well as samples enriched in synaptosomes will be investigated by nanoLC-MS/MS.

Preliminary data of the frontal cortex whole cell and synaptosome proteome show that several proteins have altered abundance in female Brd1<sup>+/-</sup> mice compared to their wild type littermates. Ingenuity Pathway analysis for whole cell data show that differentially abundant proteins are involved in neuronal development (p=0.0099) and morphology (p=0.0178) as well as in excitation (p=0.0196), while in the synaptosome, enriched pathways are involved in neuronal morphogenesis (p=0.0022) and long-term potentiation (p=0.0022). Differentially abundant proteins show enrichment for schizophrenia risk proteins (p=0.0477) in the proteome data and mood disorders (p=0.0236) in the synaptosome dataset.

This study will help us explain the observed phenotypes in the Brd1<sup>+/-</sup> mice on a molecular level. This new information could lead to new candidate proteins, helping us to unravel the pathogeneses of SZ and BD.

#### CH.14 Kristian Krogh EFFECTIVE DEBRIEFING APPROACHES IN SIMULATION BASED EDUCATION

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Introduction: Debriefing facilitates participants' learning from the simulated experiences through reflection and feedback. The value of debriefing post scenario in simulation-based education (SBE) has been well documented. Though the literature describes what constitutes effective debriefing, there is limited information as to how experts or experienced debriefers practice. This study explores the practice of expert debriefers, who work within full-scale high-stakes immersive SBE.

Methods: Individual semi-structured interviews were conducted with experts in debriefing after immersive simulation based education.

Respondents were nominated by peers through purposive sampling across Australian states. Interviews were audio recorded and transcribed for thematic analysis.

Results: A total of 24 interviews of 45-95 minutes were transcribed. Participants were from all states of Australia, with 20 different workplaces and centres, 6 different disciplines and 14 sub-disciplines. The three high order categories are: features of expert practice; the development of expertise; and the influence of context upon debriefing practice. Analysis is indicating that dominant practice features include: debriefing models used; video assisted debriefing; briefing; and continued professional development.

Discussion and conclusions: This study looks at the self-reported practices of expert debriefers. The purposive sampling covered a large range of disciplines and no new themes (saturation) were introduced within the final interview set. Interviewed expert debriefers do not use a single model for practice but have blended approaches to debriefing with genuine interest and honesty as the main drivers.

CH.15      Anne Dorte  
Blankholm

#### PREOPERATIVE PLANNING OF RENAL TRANSPLANTATION: A COMPARISON OF NON-CONTRAST-ENHANCED ULTRASONOGRAPHY, COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE ANGIOGRAPHY WITH OBSERVATIONS FROM SURGERY

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Purpose: The aim of this study was to identify the optimal preoperative imaging modality for the examination of vessel status without the use of contrast agents in kidney transplant candidates.

Material and methods: Fifty-three consecutive patients were examined, including 30 males and 23 females.

Ultrasonography (US), non-contrast-enhanced computed tomography (NCCT) and non-contrast-enhanced magnetic resonance angiography (NCMRA) were compared using inspection during kidney transplantation (TX) as a reference standard. The sensitivity and specificity to severe arteriosclerotic changes and the accuracy were calculated. Kappa statistics were used to assess the agreement between examination modalities, and McNemar's test was used to test for significant differences.

Results: US had higher sensitivity (1.0) and better agreement with surgery (k=0.89) than both NCCT (sensitivity=0.60; k=0.72) and NCMRA (sensitivity=0.20; k=0.30). No significant difference was found between TX

and US ( $p=0.3173$ ) or TX and NCCT ( $p=0.1573$ ), but there was a significant difference between TX and NCMRA ( $p=0.0455$ ).

Conclusion: Either US or NCCT can be used as the preferred preoperative imaging modality to examine vessel status before kidney transplantation, but a combination of the two is preferable. NCMRA should not be used as the sole imaging modality for this purpose, because of its low sensitivity in detecting severe arteriosclerotic disease without the presence of stenosis.

CH.16 Helene Tilma RECENT NIGHT-SHIFT WORK AND RISK OF BREAST CANCER  
Visitisen

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Objectives: Experimental evidence suggests a short term effect of light at night on breast cancer oncogenesis. We studied the short term effect of night work on breast cancer.

Method: We established a large, national cohort of employees in the public health care sector with a high prevalence of night shift work and with detailed data regarding occupational title and date, hour, and minute for the beginning and end of every work duty up to six years prior to index data: The Danish Working Hour Database (DWHD). DWHD encompasses payroll data as of 2007. From study entry exposure to night-shifts was quantified in two ways to capture cumulated exposure and intensity of exposure: 1) the cumulated number of days with night-shifts since study entry, 2) the cumulated number of night-shifts the last 365 days. Looking at both the exposure status at the specific days and the exposure status 365 days before the specific day (one-year-lag). Information on covariates was obtained from registry linkage.

Results: The 6-year follow up from 2007 to 2012 included 159,569 women contributing to a total of 771,417 person years and 1,245 breast cases. The exposure metrics showed decreasing covariate adjusted rate ratios of breast cancer by increasing number of night-shifts within the recent six years as well as recent 365 days. These trends were significant for the cumulated night-shifts the past 365 days when no lag-time was accounted for.

Conclusion: We found no association between recent night-shift work and breast cancer risk. This was regardless of cumulated number of night-shifts or the intensity of night-shifts.



- CH.17 Christian Bo Poulsen INDUCTION OF PERTURBED SHEAR STRESS LEADS TO FOCAL ADVANCED ATHEROSCLEROTIC PLAQUE FORMATION IN TRANSGENIC MINIPIGS WITH HYPERCHOLESTEROLEMIA

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Background: Low shear stress (LSS) has been associated with initiation and progression of coronary atherosclerosis (AS). Imposing persistent LSS in the coronary arteries of hypercholesterolemic mini-pigs could induce advanced coronary AS, including thin cap fibroatheroma (TCFA).

Methods: Five female Yucatan D374Y-PCSK9 transgenic hypercholesterolemic mini-pigs were implanted with a shear-modifying stent in the LAD (n=1) or LCx (n=4). The un-instrumented coronary artery served as the control. Angiography, Doppler flow velocity and optical coherence tomography (OCT) were performed in both instrumented and control arteries at baseline, 18 and 36 weeks after implantation. Following euthanasia, coronary arteries were excised and sectioned at 3µm intervals. The lumen was reconstructed from in vivo OCT images and computational fluid dynamics simulations were performed to calculate change in LSS over time. Digitized histological sections were co-registered with the reconstructed lumen at each time point, allowing calculation of the overlap between changes in LSS over time and plaque burden.

Results: All pigs developed advanced AS downstream of the stent including TCFA(N=2). Intima area (N=5, mean±SE) post stent was significantly increased compared to the control artery ( $1.85 \pm 0.69$  versus  $0.34 \pm 0.15 \text{ mm}^2$ ,  $p<0.01$ ). Local regions of high plaque burden overlapped with persistent reduction in LSS, with values at 18 and 36 weeks of  $74.76 \pm 4.52\%$  and  $62.18 \pm 15.40\%$ , respectively, which was significantly higher than the overlap observed at baseline ( $1.51 \pm 0.79\%$ ,  $p<0.02$ ).

Conclusion: Imposing LSS in the coronary arteries of D374Y-PCSK9 mini-pigs promotes focal advanced AS including TCFA.

- CH.18 Mette Lausten Hansen OCCUPATIONAL PREDICTORS OF SICK LEAVE DURING PREGNANCY - RESULTS FROM A POPULATION-BASED COHORT STUDY

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Background: Sick leave during pregnancy is frequent. A range of occupational exposures and trades are associated with sick leave in pregnancy, but studies are often limited by inadequate measures of exposure and possible confounding.

Objective: To investigate associations between work postures, lifting at work, shift work, work hours and job strain and the risk of sick leave in pregnancy.

Methods: We used data from The Danish National Birth Cohort (DNBC) and from the Danish Register for Evaluation of Marginalisation (DREAM). DNBC contains 100,418 pregnancies. Pregnant women were interviewed twice during pregnancy and provided information on occupational exposures and potential confounders. Women with gainful employment, singleton-pregnancies, without an obstetric event one year before the DNBC pregnancy and with a chronological sequence of interviews were included, leaving a study population of 51,874 women. First episode of sick leave from 10 to 29 completed pregnancy weeks was the outcome; data were obtained from DREAM. Data were analysed by a Cox regression model, adjusting for a range of important potential confounders.

Results: The majority of working conditions were associated with increased hazards of sick leave. For non-sitting work postures ( $HR_{\text{range}}: 1.22-1.63$ ), cumulative lifting ( $HR_{>1000 \text{ kg}}: 1.66$ ; 95% CI (1.40-1.97);  $HR_{\text{trend}}: 1.07$ ; 95% CI (1.05-1.10)), shift work ( $HR_{\text{evening}}: 1.34$ ; 95% CI (1.21-1.47);  $HR_{\text{night}}: 1.42$ ; 95% CI (1.01-1.98)), and high job strain ( $HR: 1.35$ ; 95% CI (1.26-1.45)).

Conclusions: These results are in agreement with previous studies and suggest that initiatives to prevent sick leave during pregnancy should be based on working conditions.

CH.19 Sara Heebøll PLACEBO-CONTROLLED CLINICAL TRIAL: LONG-TERM RESVERATROL TREATMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE

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Background: 'The obesity epidemic' has led to an increase in obesity-related conditions like non-alcoholic fatty liver disease (NAFLD), for which effective treatments are in demand. The polyphenol resveratrol (RSV) prevents the development of experimental NAFLD in vitro and in vivo due to anti-inflammatory, anti-oxidant and AMPK/SIRT1 activating effects. Here, we hypothesized that RSV could alleviate NAFLD in a double-blind, placebo-controlled, clinical trial.

Methods: 28 overweight, non-diabetic patients with transaminasemia and

histological NAFLD were recruited for the trial and randomized to placebo or RSV 500 mg t.i.d. for 6 months. 26 patients completed the trial and underwent repeated clinical investigation, blood work and MR spectroscopy. 19 patients also committed to a repeated liver biopsy.

Results: We detected no difference in ALT ( $P=0.51$ ) or the level of other plasma markers of liver injury in between the RSV and placebo group. Similarly, we observed no improvements in the metabolic syndrome (central obesity, plasma lipids, glucose tolerance, blood pressure). There was a decrease in liver steatosis as assessed by MR spectroscopy in RSV treated patients from 31%-23% ( $P=0.03$ ), however no statistical difference between the treatment groups ( $P=0.38$ ). A RSV-mediated decrease in steatosis was also seen in the histological evaluation, however there was no statistical difference between the groups ( $P=0.22$ ). Also, RSV did not improve NAFLD activity score ( $P=0.98$ ) or fibrosis ( $P=0.75$ ).

Conclusion: Contrary to findings in experimental steatosis, high-dose, long-term RSV treatment had no consistent therapeutic effect in alleviating clinical and histological NAFLD.

CH.20 Maria Charlotte Steffensen HYPERCORTISOLISM IS PREVALENT IN NEWLY DIAGNOSED TYPE 2 DIABETES: A PROSPECTIVE STUDY OF 505 CONSECUTIVE PATIENTS

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Background: Cross-sectional studies indicate that a relatively high number of patients with type 2 diabetes (T2D) has undiagnosed and/or subclinical Cushing Syndrome (CS). This may have therapeutic implications, but it remains dubious if screening for CS in T2D is recommendable.

Aim: To investigate the prevalence of CS in a large, unselected cohort of newly diagnosed T2D patients.

Methods: 505 consecutive outpatients with T2D were screened for hypercortisolism by means of 23:00 salivary cortisol (SC) as well as a 1 mg overnight dexamethasone suppression test (OD). Patients who did not suppress  $\leq 50$  nmol/l 12 hours after 1 mg OD were further examined with 48 h low dose dexamethasone suppression test (LDDST) and 24-h urinary free cortisol collection (UFC).

Results: 85 (16.8%) patients had elevated cortisol after screening with 23:00 SC and 1 mg OD. 20 of these failed to suppress serum cortisol after 48 h LDDST and/or had elevated UFC. 42 patients had normal cortisol after initial screening. Comparing these 42 patients with the 20 patients with subsequent hypercortisolism, we found no significant difference in age, BMI, HbA1c or blood pressure. Of the 20 patients (4 %) with manifest hypercortisolism, subsequent imaging with either pituitary MR or abdominal CT according to suppressed ( $n=8$ ) or normal/elevated ( $n=12$ ) ACTH levels revealed one pituitary macroadenoma and 9 adrenal adenomas.

Conclusion: 1) The prevalence of hypercortisolism in unselected newly diagnosed T2D ranges between 4 and 16 % depending on the screening algorithm, 2) Hypercortisolism was not associated with a distinct phenotype, and 3) The therapeutic and prognostic implications must await longer-term follow-up.

CH.21      Navid      QUANTITATIVE PROTEOMICS REVEALS METABOLIC REPROGRAMMING IN  
Sahebekhtiari      ETHE1 DEFICIENT MICE

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Deficiency of mitochondrial sulfur dioxygenase (ETHE1) causes the severe metabolic disorder ethylmalonic encephalopathy, which is characterized by early-onset encephalopathy and defective cytochrome C oxidase because of hydrogen sulfide accumulation. A Biochemical hallmark is high concentration of ethylmalonic acid in urine which also is characteristic of the fatty acid beta-oxidation defect short chain acyl CoA dehydrogenase deficiency. Although the severe systemic consequences of disease are becoming clear, the molecular effects are not well known, therefore we performed a large scale quantitative proteomics study for further elucidating the effects of ETHE1 deficiency. Peptide labeling with iTRAQ was performed on six wild type and KO mice then identified and quantified by nLC-MS/MS. DAVID and STRING were used to identify enriched functional annotation terms and clustering. Down-regulation of several proteins related to oxidation-reduction, such as different dehydrogenases, cytochrome P450 members and those active in oxidative stress response like catalase and glutathione S transferase, indicate clear links between ETHE1 deficiency and redox active proteins. The ETHE1 deficiency was also shown to alter the cellular energy metabolism in the form of up-regulation of enzymes active in glycolysis such as aldolase and pyruvate kinase together with the gluconeogenetic pyruvate carboxylase, which all in all confirmed cellular regulation to compensate the lack of energy due to electron transport chain corruption. Our data suggest that ETHE1 deficiency is clearly linked with alteration in levels of several redox active proteins and also reprogramming in metabolic pathways.

CH.22      Anne Kristine      MELATONIN IMPROVES BONE MINERAL DENSITY (BMD) AT THE FEMORAL  
Amstrup      NECK IN POST-MENOPAUSAL WOMEN WITH OSTEOPENIA: A  
RANDOMIZED CONTROLLED TRIAL

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Background: Melatonin is known for its regulation of circadian rhythm. However, over the recent years, studies have shown that melatonin also may affect bone by increasing osteoblast differentiation and inhibiting osteoclast activity. The production of melatonin decreases by age, and it is unknown whether decreased melatonin levels in the elderly may be associated with increased bone loss. We aimed to investigate whether treatment with melatonin may improve BMD.

Method/design: In a double-blind placebo-controlled study, we randomized 81 healthy post-menopausal women with osteopenia to 12 months of treatment with melatonin in a daily dose of 1 mg (N=20), or 3 mg (N=20), or placebo (N=41). All participants also received a daily supplement of 800 mg of calcium and 20 mg of vitamin D3. BMD was measured by DXA at baseline and after 12 months of treatment.

Results: Mean age of the women was 63 years (range 56-73). Compared with placebo, BMD at the femoral neck increased by 1.7% in response to melatonin ( $p<0.05$ ). A dose-response relationship was present ( $p<0.01$ ) as femoral neck BMD decreased by 1.6% in the placebo group, by 1.0% in the 1 mg melatonin group, whereas BMD increased by 1.3% in the 3 mg melatonin group. Treatment did not affect BMD significantly at the lumbar spine, or whole body. Melatonin did not change body weight, but did affect body composition. Compared with placebo, melatonin decreased fat mass by 7.7% ( $p<0.01$ ), while lean body mass increased by 2.5% ( $p=0.05$ ).

Conclusion: One year of treatment with melatonin improved BMD dose-dependently at femoral neck and showed beneficial effects on body composition in terms of a reduced fat mass and increased lean tissue.

CH.23      Christian Bjerregaard Olesen      EXTRACTION OF PERFLUORINATED ALKYL ACIDS FROM HUMAN SERUM FOR DETERMINATION OF THE COMBINED XENOESTROGENIC TRANSACTIVITY: A METHOD DEVELOPMENT

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Humans are exposed to perfluorinated alkyl acids (PFAAs) through food, drinking water, consumer products, dust, etc. The human metabolism and excretion of the long-chain PFAAs is slow with half-lives up to 8.8 years. Studies suggest that the PFAAs are potential endocrine-disrupting compounds that might affect human health.

We developed a method for extraction of PFAAs from human serum with simultaneous removal of endogenous sex hormones. The developed method includes solid phase extraction, liquid/liquid extraction, HPLC fractionation and weak anion exchange. The method was validated by extraction of seven persistent PFAAs spiked to human male serum obtaining mean recoveries between 49.6-78.6%. Using an estrogen receptor (ER) transactivation luciferase reporter gene assay, analysis of the

extracted PFAA serum fraction from three pregnant women showed the ER-active endogenous hormones were removed.

The developed method was further documented by extraction of the PFAAs from the serum of 18 Danish pregnant women. The PFAA fraction from three of the 18 samples significantly induced the ER-transactivity. Upon co-exposure with the natural ER-ligand 17 $\beta$ -estradiol (E2), 17 of the 18 PFAA fractions caused a significant further increase of the E2 induced ER-transactivity. In conclusion, we developed a method to extract PFAAs from human serum, and the method documentation suggested that PFAAs at the levels found in human serum can transactivate the ER.

CH.24 Christian Lottrup

## FUNCTIONAL PROPERTIES OF THE OESOPHAGUS IN BARRETTS OESOPHAGUS PATIENTS

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**Introduction:** The underlying pathophysiology behind Barrett's oesophagus is still not fully known, but oesophageal sensitivity has previously been shown to be decreased and acid clearance has been shown to be impaired.

**Aims and methods:** We aimed to investigate functional properties in BO patients using a multi-faceted assessment. Upper endoscopy, distensibility testing with the Functional Lumen Imaging Probe (FLIP), hydrochloric acid clearance assessment, and multimodal pain stimulation were applied to the oesophagus. Thirty patients with BO were compared to fourteen healthy controls.

**Results:** The lower esophageal sphincter in BO patients had a significantly lower pressure and was more distensible (both  $P < 0.001$ ) than the common oesophago-gastric junction in controls. When swallowing randomly, the swallowing frequency was significantly higher ( $P < 0.01$ ) and acid clearance time was significantly shorter ( $P = 0.01$ ) in BO patients compared to controls. For multimodal pain stimulation, when considering the stimulus required to reach moderate pain (VAS = 7), BO patients were hyposensitive to mechanical ( $P = 0.006$ ) and electrical stimulation ( $P = 0.03$ ), but hypersensitive to acid stimulation ( $P = 0.03$ ).

**Conclusion:** BO patients showed increased distensibility of the oesophago-gastric junction and a faster acid clearance time when swallowing randomly. BO patients were hyposensitive to mechanical and electrical stimulation, but hypersensitive to acid stimulation. These results are to some degree different from earlier findings. The finding of hypersensitivity and shorter acid clearance time in BO patients could indicate a sensitisation to

acid because of underlying oesophagitis.

- CH.25      Maj Høygaard      COMPARISON OF FATIGUE RESISTANCE AND FAILURE MODES BETWEEN  
Nicolaisen      METAL-CERAMIC AND ALL-CERAMIC CROWNS BY CYCLIC LOADING IN  
WATER

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Objectives: To compare fatigue resistance and fracture mode of metal-ceramic crowns with all-ceramic crowns under compressive cycling loading in water.

Methods: Twenty specimens of ivory were randomized and individually prepared to receive anatomically shaped metal-ceramic (n=10) or all-ceramic crowns (n=10). All steps in production were equivalent to clinical situations. Resistance to fatigue fracture was tested under compressive cyclic loading using a universal testing machine, with a loading frequency of 12 Hz using a spherical tungsten carbide indenter (6 mm diameter) in distilled water. The maximum compressive load was increased as the number of cycles increased (600,000 cycles at 400 N, 200,000 cycles at 600 N, 200,000 cycles at 800 N and 200,000 cycles at 1,000 N). The specimens were inspected after each loading sequence for initial failures such as infractions. Final failure was considered as any loss of material which automatically ended the test and the number of cycles until final failure was recorded. Fractographic analysis of the fractured specimens was performed with scanning electron microscopy (SEM).

Results: The two types of crowns exhibit similar fatigue resistance ( $P=0.87$ ) to compressive cycling loading under wet conditions. The failure modes as observed with SEM were similar in the two groups and were found in the veneer ceramics, except that three all-ceramic crowns displayed a complete framework fracture.

Conclusions: Within the limitation of this study using simulated oral masticatory function, the results revealed that the fatigue resistance was similar for the two crown types.

- CH.26      Sepp de Raedt. THE DYSPLASTIC PELVIS: A STATISTICAL SHAPE MODEL

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It is commonly accepted that hip dysplasia is characterized by a shallow acetabulum with insufficient coverage of the femoral head. Previous work

has shown that a large variation exists within hip dysplasia and that understanding this complex morphological variation is important to obtain optimal reorientation during periacetabular osteotomy (PAO). The aim was therefore to gain a better understanding of the shape variation by creating a three-dimensional model of the dysplastic pelvis.

CT images were retrospectively collected from patients who underwent CT investigation prior to PAO. A statistical shape model was constructed by segmenting the pelvis and establishing point correspondences. Manual diagnostic angle measurements were performed.

Seventy-five patients (24 male) were included. The main modes of variation describe the difference in shape due to gender and the varying degrees of hip dysplasia. The first mode illustrates known gender differences: pelvic size, pubic arch angle, and retroversion of the acetabulum and was significantly different by gender (Diff: 1.7, 95% CI: 1.4;2.0, P-value: <0.0001). The second mode describes a change from a horizontal acetabular roof to a steep roof typical of hip dysplasia and was significantly different (Diff: 0.5, 95% CI: 0.2;0.8, P-Value: 0.0008) for dysplastic hips (CE<25 and AI>10). No statistically significant difference was found with respect to gender (P-value: 0.9).

Initial results show the relationship between pelvic shape, gender, and manual angle measurements. However, future work will investigate the relationship with shape and outcome variables such as pain, later arthroscopy or conversion to total hip replacement.

## CH.27 Mette Winther PROGNOSTIC FACTORS IN GASTROESOPHAGEAL CANCER: HYPOXIA AND MICRORNA CORRELATION

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Background: Prognostic and predictive factors are needed to improve patient survival in gastroesophageal cancer.

Aim: The aims were to identify clinicopathological parameters as prognostic factors including a subset of hypoxia-responsive genes and to identify hypoxia-correlated miRNAs.

Material and methods: Ninety-five patients with loco-regional gastro-esophageal cancer were retrospectively analyzed. Gene expression on 15 hypoxia-responsive genes was obtained from formalin-fixed paraffin-embedded, diagnostic biopsies and measured by qPCR. Microarrays were used to quantify miRNAs and Significant Analysis of Microarray (SAM) to elucidate hypoxia-correlated miRNAs.

Results: Pathological complete response (pCR) was identified as a prognostic factor for disease-specific survival in esophageal squamous cell carcinoma (ESCC) (HR= 0.21 (CI:0.05-0.95), P=0.04). An unsupervised hierarchical clustering of hypoxia-responsive genes showed two well-



differentiated patient clusters with tumors of more or less hypoxic genotypes. Only patients with ESCC (n=51) showed intra-group heterogeneity. In contrast, patients with adenocarcinomas of the esophago-gastric junction and stomach were classified as less hypoxic, indicating that the hypoxic impact in ESCC is more profound. The most hypoxic third of ESCC showed a trend towards a poorer outcome in terms of overall survival (HR= 0.48 (CI:0.21-1.07), P=0.07). Applying SAM, 35 miRNAs were significantly up-regulated in the group of more hypoxic tumors, including miR-210 and miR-21.

Conclusion: In ESCC, pCR was identified as a prognostic factor and hypoxia a promising prognostic marker. A subset of miRNAs was correlated with the hypoxic status in ESCC.

CH.28      Aida Solhøj  
Hansen      SIGNIFICANCE OF CD46 ISOFORMS FOR ENTRY OF HUMAN HERPESVIRUS-6B

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CD46 is a glycoprotein expressed on the surface of all nucleated human cells. Among other functions, CD46 acts as a cellular receptor for human herpesvirus-6B (HHV-6B), a virus that is causing the childhood disease exanthema subitum and is associated with certain neuropathologies. Although HHV-6B may infect a broad range of cells, it prefers to replicate in CD4+ T lymphocytes. Alternative splicing produces multiple isoforms of CD46, and we hypothesize that the separate isoforms may have different functions for HHV-6B infection and thereby play a role in the tropism of HHV-6B.

Seven different T-cell lines were infected with HHV-6B, and the level of infection was analysed by real-time PCR of the expression of the viral transcripts U7 and U23 and by western blotting of the viral protein DR6. In addition, the surface expression of CD46 was determined by flow cytometry and the relative mRNA expression of the separate CD46 isoforms analysed by real-time PCR.

These data demonstrated a difference in the level of U7 and U23 as well as DR6 between the cell lines upon infection, indicating a difference in how efficiently they were infected with HHV-6B. The cell lines were observed to have equal expression levels of CD46 on their surface. Interestingly, the determination of expression of the separate CD46 isoforms showed that the cell lines with the highest level of infection have a higher relative expression of the CD46 isoforms C1 and C2 compared to the poor infected cell lines.

In conclusion, a difference in how efficiently the T-cell lines were infected by HHV-6B was observed and this seemed to correspond to a difference in the expression pattern of the separate CD46 isoforms.

CH.29      Sofie      DISTURBANCES OF CIRCADIAN RHYTHMS IN AN ANIMAL MODEL OF

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Clinical data from depressed individuals shows that physiological states and mood changes are consistent with disturbances in circadian related processes. The suprachiasmatic nucleus (SCN) is well known for its function as the master clock and regulates several circadian systems by clock gene expression. In addition to central expression, peripheral clock genes have been found.

The study is based on a highly validated animal model of depression, the chronic mild stress (CMS) model. 8 depression-like rats and 8 control rats were killed by decapitation every 4 h within a 24 h period. Trunk blood, brain and liver tissue were collected. Core body temperature was measured with a rectal probe prior to decapitation. The amount of plasma corticosterone and melatonin were quantified using an ELISA and RIA kit, respectively. Identification of specific clock genes in the liver was done using the Q-PCR method. Quantification and visualization of clock genes in the brain were established by the in situ hybridization method.

We studied three of the most essential clock genes, *Per1*, *Per2* and *Bmal1*, and found that the effect of CMS on clock gene expression was selective and region specific. However, the *Per1* expression was partly protected against stress. We found an increased level of corticosterone and melatonin in the depression-like animals as well as a shifted circadian rhythm. Further, CMS did not abolish the circadian rhythm of the phase markers, but induced shifts in peak levels for melatonin and core body temperature and induced an additional corticosterone peak.

CH.30      Gro Helen Dale ASSESSING THE EFFECT OF METHYLPREDNISOLONE IN ACUTE OPTIC NEURITIS

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Background: Optic neuritis (ON) is an inflammatory disease that can result in irreversible retinal thinning and correlated permanent visual loss. It is unknown whether intravenous methylprednisolone (IVMP) can protect the retinal cell-layers.

Aim: To assess the effect of treatment with IVMP on visual function and retinal thinning in acute ON.

Material and methods: Forty-three patients were examined at baseline and six months with best corrected visual acuity (BCVA), contrast sensitivity test, Rayleigh match color test, latency to P100 and OCT. The latter consisted of

a scan of the peripapillary retinal nerve fiber layer thickness (RNFLT) and of the total macular volume (TMV). Treatment was offered when BCVA was  $\leq 0.5$  and symptoms had lasted for  $\leq 14$  days. Data was analyzed with Wilcoxon ranksum test, unpaired ttest and Fisher's exact test.

Results: Nineteen patients (44%) received treatment. At six months, there was a significant difference between the treated and non-treated group in contrast sensitivity (mean: 1.3 vs 1.5 log;  $p=0.004$ ), but not in BCVA ( $p=0.11$ ) or Rayleigh match ( $p=0.17$ ). The latency to P100 was prolonged in both groups, but worse in the treated (mean: 146.3 vs 126.4 msec;  $p=0.019$ ). RNFLT and TMV were generally reduced, with no significant difference between the groups (RNFLT:  $p=0.078$ ; TMV:  $p=0.074$ ).

Excluding five patients who had BCVA  $\leq 0.5$  but were not treated, and two patients who experienced a new ON, revealed a significant difference between the groups in RNFLT (mean: 74.6 vs 88.5  $\mu\text{m}$ ,  $p=0.0064$ ). However, the treated group had the worst outcome.

Conclusion: Treatment of acute ON with IVMP does not seem to affect the visual function or prevent retinal thinning.

CH.31 Maryam  
Ardalan

# STRUCTURAL ALTERATION OF HIPPOCAMPUS AND SUSTAINED ANTIDEPRESSANT EFFECT OF KETAMINE

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Background: The glutamatergic system and the structural plasticity hypothesis for sustained antidepressant effect are principal components of novel antidepressant therapeutics. In this study, design-unbiased stereological methods are used to test the structural plasticity hypothesis of hippocampus for sustained antidepressive effect of single Ketamine injection.

Material and methods: A single intraperitoneal injection of Ketamine (15mg/kg) or saline was given to the Flinders Sensitive Line and Flinders Resistant Line rats, and they were perfused 7 days after treatment. By using the physical dissector, the numerical density of synapses was estimated. The optical fractionator was used to estimate microvessel length with global spatial sampling method. The volume of different subfields of hippocampus was estimated by using the Cavalieri estimator.

Results: The volume of hippocampal subfields is larger in the FRL-Veh rats when comparing to FSL-Veh rats and the FSL-Ket versus FSL-Veh rats. A significantly higher number of spine synapses was found in FSL-Ket rats in comparison with FSL-Veh rats. More specifically, we found no significant

changes in the number of perforated and shaft synapses between FSL-Ket and FSL-Veh groups, while the number of non-perforated synapses was significantly higher in the FSL-Ket versus FSL-Veh group. Microvessels in FSL-Veh rats were significantly shorter than in the control group. Interestingly, the length of the microvessels was significantly increased in FSL rats one week after ketamine treatment.

Conclusion: Our results support the hypothesis that the structural plasticity is one of the mechanisms underlying the sustained antidepressant effect of ketamine.

CH.32      Abhishek  
Kumar

## ROLE OF PERIODONTAL MECHANORECEPTORS IN BEHAVIORAL LEARNING AND SKILL ACQUISITION DURING ORAL FINE MOTOR FUNCTION

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Background: Mastication is a complex motor task. The brain assimilates and organizes sensory information from various orofacial mechanoreceptors to optimize oral functions.

Objective: To test the effect of short-term training and the role of periodontal mechanoreceptors in behavioral learning and skill acquisition during oral fine motor function.

Methods: 30 healthy volunteers were equally divided into intervention and control group. The participants (in both the groups) were asked to perform 3 series each of the behavioral task before and after a short-term training. The behavioral task was to manipulate and split a chocolate candy into two equal halves. The short-term training involved extensive practice of the task with feed-back on the performance of the task and motivating the participants to perform better. Further, the upper and lower anterior teeth of the participants were anesthetized in the intervention group and 3 series of the behavioral task were performed while the control group performed the three series without the anesthesia. The performance of the task was assessed by the weighing largest piece of the candy resulting from the split and comparing with the half of the weight of the candy.

Results: (preliminary) The precision of the task performance increased significantly after the short-term training ( $P < 0.05$ ). However, there was a significant decrease in performance on anesthetizing the tissues around the periodontium.

Conclusion: The preliminary results suggest that periodontal mechanoreceptors may provide important sensory information and may have an active role in behavior learning and skill acquisition during oral fine motor function.

CH.33      Anette Riisgaard Ribe      LONG-TERM MORTALITY OF PERSONS WITH SEVERE MENTAL ILLNESS AND DIABETES

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Background: Persons with severe mental illness (SMI) have an excess mortality, which may partly be explained by the high prevalence of diabetes among these persons. The aim was to assess the overall and cause-specific mortality of persons with SMI and diabetes in a large population-based cohort.

Methods: We compared the overall and cause-specific mortality in persons with SMI and diabetes with that of the general Danish population between 1997 and 2009 by linking data from Danish national registries.

Results: The cohort counted 4,734,703 persons of whom 37,389 had SMI, 248,176 had diabetes, and 4,284 had SMI and diabetes. During follow-up, 651,080 persons died of whom 1,083 persons had SMI and diabetes. The overall mortality rate ratios (MRRs) for persons with SMI and diabetes were 4.14 (95% confidence interval (CI) 3.81-4.51) for men and 3.13 (95% CI 2.88-3.40) for women as compared with the background population. The cause-specific MRRs were lowest for malignant neoplasms (women: MRR=1.98, 95% CI 1.64-2.39; men: MRR=2.08, 95% CI 1.69-2.56) and highest for suicide among women (MRR=12.31, 95% CI 6.80-22.28) and accidents among men (MRR=7.89, 95% CI 5.51-11.29). The cumulative risks of death within seven years of diabetes diagnosis were 15.0% (95% CI 12.4-17.6) for those younger than 50 years, 30.7% (CI:27.8-33.4) for those aged 50-69 years, and 63.8% (95% CI 58.9-68.2) for those aged 70 years or older.

Conclusions: The long-term mortality is high for persons with SMI and diabetes. This calls for effective intervention from a coordinated and collaborating healthcare system.

CH.34      Lu Xing      GENDER DIFFERENCE EFFECT ON RENAL AQP1-3 EXPRESSION PATTERNS IN RESPONSE TO PARTIAL UNILATERAL URETERAL OBSTRUCTION

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Background: Both the overall prevalence of congenital urinary tract defects at birth and congenital hydronephrosis are higher among males than among females. AQP1-3 involves in the mechanism of pathophysiologic

changes in obstructed kidney; however, how the gender difference response to PUUO in newborn rats before the nephrogenesis completed is still unclear.

Objective: To investigate gender difference effect on renal AQP1-3 expression to the duration of PUUO for 1 week in neonatal rats.

Methods: Twenty-four newborn rats were allocated into 2 groups randomly: PUUO (n = 12, 6 males, 7 females) and Sham (n = 12, 6 males, 6 females). The left kidney was subjected to PUUO within 2 days of birth. Sham group was analyzed in parallel. One week after PUUO, the kidneys were harvested.

Results: AQP1 protein abundance was lower in male than in female in PUUO1W-RK kidney. Downregulation of AQP2-3 protein was only observed in male in PUUO1W-LK group compared to Sham. In PUUO1W-LK group, AQP2 expression was lower in male than in female. Immunohistochemistry staining of renal AQP1 showed weaker labeling in male compared to female in PUUO1W-RK group. In male rats, AQP2-3 showed weaker labeling of PUUO1W-LK group compared to Sham. In PUUO1W-LK group, AQP2 labeling was weaker in male than in female.

Conclusion: The present study demonstrated the downregulation of AQP2 and AQP3 in response to neonatal PUUO for 1 week mainly occurred in male rats in the obstructed kidney. The lower expression of AQP2 in male rats compared to female in response to neonatal PUUO may be due to the effect of female steroid hormone estrogen.

Key words: AQP1-3, newborn rats, PUUO, kidney, gender difference

CH.35 Louise Bill

HYPONATREMIA IS HIGHLY PREVALENT AND ASSOCIATED WITH INCREASED MORTALITY RISK INDEPENDENT OF UNDERLYING DISEASE AND SEVERITY OF HYPONATREMIA: A COHORT STUDY OF 279,508 PATIENTS ACUTELY ADMITTED TO DEPARTMENTS OF INTERNAL MEDICINE

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Background: Data on the existence of a dose-response relation between hyponatremia and mortality risk are conflicting.

Objectives: To examine the effect of admission hyponatremia severity on 30-day and 1-year mortality overall and by diagnostic groups of previous morbidity and primary discharge diagnosis.

Design: Cohort study using prospective data from population-based registries.

Patients: All 279,508 first-time acute admissions to departments of internal

medicine in the North and Central Denmark Regions in 2006-2011.

Analyses: Prevalence. 30-day and 1-year mortality. Relative risks (RRs) with 95% confidence intervals (CIs), adjusted for age, gender, and previous morbidities, and stratified by diagnostic subgroups. Probability of death, treating serum sodium as a continuous variable.

Results: The prevalence of admission hyponatremia was 15%. Thirty-day mortality was 3.6% in normonatremic patients compared to 7.3%, 10.0%, 10.4% and 9.6% in patients with serum sodium of 130-134.9mmol/l, 125-129.9mmol/l, 120-124.9mmol/l, and <120mmol/l, resulting in adjusted RRs of 1.4 (95%CI: 1.3-1.4), 1.7 (95%CI: 1.6-1.8), 1.7 (95%CI: 1.4-1.9) and 1.3 (95%CI: 1.1-1.5), respectively. One year after admission the risk was increased by 30-40%. Mortality risk was increased across virtually all diagnostic groups. The probability of death increased steeply for sodium values from 139mmol/l to 132mmol/l, below which no clear increase was observed.

Conclusion: Hyponatremia is highly prevalent among patients acutely admitted to internal medicine departments, and associated with increased 30-day and 1-year mortality risk irrespective of underlying disease. The risk seems independent of degree of hyponatremia.

CH.36 Anne Vestergaard

NORMAL TISSUE SPARING IN AN ADAPTIVE RADIOTHERAPY TRIAL FOR URINARY BLADDER CANCER

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Purpose: This study reports dose/volume outcome from the first twenty patients treated in our multicenter clinical phase II trial of daily adaptive radiotherapy for bladder cancer.

Methods and materials: All patients received 60 Gy in 30 fractions to the bladder; in 13 of the patients the pelvic lymph nodes were simultaneously treated to 48 Gy. Daily patient set-up was by use of cone-beam CT (CBCT) guidance and treatment was delivered by volumetric modulated arc therapy (VMAT). The first five fractions were delivered using large, population-based margins; the bladder contours from the CBCTs acquired prior to the first four fractions were used to create a library of three plans, corresponding to a small, medium and large size bladder. All patients were from fraction no. 6 treated using daily online plan selection, where the smallest plan covering the bladder was selected prior to delivery of each treatment fraction. The course-averaged PTV (PTV<sub>course</sub>) for ART was calculated. The sparing of normal tissue was quantified in relation to the non-adaptiv RT in terms of both relative and absolute volume reduction.

Results: The library plans were selected almost equally often, with a mean of 10, 9 and 11 for the small, the medium and the large size, respectively.

The PTV<sub>course</sub> for ART was reduced with a median of 30% and range [11, 54%] compared to non-adaptive RT. A linear regression analysis showed a reduction in treated volume of 183 cm<sup>3</sup> (confidence interval 142 to 223 cm<sup>3</sup>).

Conclusion: Daily adaptive plan selection in RT of bladder cancer results in a considerable normal tissue sparing obtained in this trial is likely to translate into a decrease in gastro-intestinal morbidity.

- CH.37 Maja Ølholm Vase CD30 EXPRESSION IN POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS: PROGNOSTIC IMPLICATIONS AND OCCURRENCE
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- Posttransplant lymphoproliferative disorders (PTLDs) are potentially fatal, often Epstein-Barr virus (EBV)-driven neoplasias developing in immunocompromised hosts. Initial treatment usually consists of a reduction in immunosuppressive therapy and/or rituximab with or without chemotherapy. However, patients who relapse do poorly and new treatment options are warranted. With the introduction of the immunoconjugate brentuximab vedotin, the CD30 antigen has become an effectively targetable molecule. Therefore, we investigated the frequency and level of CD30 expression in PTLDs. We identified 108 PTLD patients diagnosed during 1994-2011, of which 62 had adequate paraffin embedded tissue for tissue microarray construction. Immunohistochemical expression of CD30 was consistently detected in all types of PTLD (overall 85.25%), including the monomorphic subtypes, and was correlated to a more favorable outcome. For diffuse large B-cell lymphoma (DLBCL)-type PTLD this was regardless of EBV-status, and remained significant in multivariate analyses. Cell-of-origin had no independent prognostic value in our series of DLBCL PTLD.

- CH.38 Jakob Kristian Jakobsen SENTINEL NODE BIOPSY IN PENILE CANCER - A NATIONAL RETROSPECTIVE STUDY FROM DENMARK
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**Introduction:** Nodal involvement is a strong prognosticator in penile cancer and lymph node staging is crucial. Sentinel node biopsy (SNB) is a promising staging tool. We present national data with long-term follow-up.

**Methods:** The study covers all SNB procedures performed in Denmark in the 11-year period 2000-2010. Patients were newly diagnosed and had either non-palpable lymph nodes in one or both groins or had a palpable mass in the groin, from which aspiration cytology was unable to detect malignancy. After injection with nanocolloid technetium, a scintigram was recorded before the surgical SNB. A gamma probe and intraoperative palpation of the inguinal wound was used for the detection of lymph nodes.

**Results:** 409 groins in 222 patients were examined by SNB. Median follow-up of survivors was 6.6 years (interquartile range: 5-10). Of 343 negative groins, eight disclosed false negative. 66 groins were positive. Sensitivity was 89% (95% CI, 80-95%) per groin and false negative rate was 11% (95% CI, 5-20%). Remarkably, four of 67 T1G1 patients had a positive SNB. 28 of 222 (13%) patients experienced complications to SNB during follow-up. Complications were encountered after 30 of 409 (7%) procedures.

**Conclusion:** Penile cancer sentinel node biopsy with a close follow-up is a reliable lymph node staging and has few complications in a national multicenter setting. Inguinal lymph node dissection, which has complication rates of 30-70%, was avoided in 76% of patients. The EAU/AUA guideline recommendation with no surgical staging of T1G1 tumors should be reconsidered.

CH.39      Søren Haack      DIFFUSION WEIGHTED MRI OF LOCALLY ADVANCED CERVICAL CANCER DURING RADIOTHERAPY - TREATMENT RESPONSE ASSESSMENT USING DIFFERENT SEGMENTATION METHODS

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Twelve patients with locally advanced cervical cancer underwent an MRI examination three times during radiotherapy (RT): 1) prior to RT 2) two weeks into external beam (EB) RT and 3) one week prior to brachytherapy (BT). DWI-MRI was included in all MRIs and ADC maps were calculated. A ROI was placed surrounding the entire torso and the standard deviation (SD) was calculated for the voxels included. A ROI was placed to contain

the cervix, lower uterus and the entire tumor. Voxels inside this ROI were included in the three segmentation methods: 1) relative-to-signal threshold using the  $b=1000 \text{ s/mm}^2$ , where Pixels with intensity  $>4 \times \text{SD}$  were identified as tumor tissue, 2) k-means clustering using  $b = 1000, 600 \text{ s/mm}^2$  and ADC map  $\text{mm}^2/\text{s}$  as input and 3) region-growing method using the  $b=1000 \text{ s/mm}^2$  image. Histogram analysis of ADC values was performed comparing the tumor pixels for each timepoint. Mean ADC and kurtosis of the ADC histogram (distinct from diffusion kurtosis) were compared across time points and segmentation methods. Assessment of treatment response is expressed as the percent change in ADC:  $\% \Delta \text{ADC} = [(\text{ADC}_{\text{RT}} - \text{ADC}_{\text{pre}}) / \text{ADC}_{\text{pre}}] \times 100$ . Results were statistically evaluated using oneway Anova (three timepoints) or Student's t-test (two timepoints). There was a significant change in mean ADC during treatment for both the SD4 and the clustering method ( $p = 0.007$  and  $p = 0.019$ , respectively). The segmented volume also changed significantly during RT for 4SD and clustering ( $p = 0.023$  and  $p = 0.003$ , respectively) but not for region-growing ( $p = 0.25$ ). There was a significant change in kurtosis from PRE-RT to EBRT for the 4SD and clustering method (Student's t-test  $p = 0.005$ ).

CH.40 Jill Rachel Mains

#### DYNAMIC CONTRAST-ENHANCED COMPUTED TOMOGRAPHY AS A BIOMARKER IN METASTATIC RENAL CELL CARCINOMA

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Background: Our preliminary results have shown that baseline perfusion calculated using dynamic contrast-enhanced computed tomography (DCE-CT) is a prognostic biomarker in metastatic renal cell carcinoma (mRCC), and that the change in blood volume from baseline to treatment week 5 predicts progression-free survival (Mains JR et al in Investigative Radiology 2014;49:601-7).

Aim: To further explore the impact of DCE-CT as a biomarker in mRCC.

Materials and methods: 69 patients with favorable or intermediate Memorial Sloan Kettering Cancer Center risk group and clear cell mRCC participating in an ongoing prospective randomized phase II trial (DARENCA-1) comprising interleukin-2-based immunotherapy and bevacizumab have been included in this analysis. All patients have a follow-up time of at least 18 months. The DCE-CT scans were performed at baseline, at weeks 5 and 10. The following DCE-CT parameters will be found: Perfusion (using 4 different methods), Blood Volume (using two different methods), Mean Transit Time, and Permeability. Parameters for DCE-CT will be correlated with sum of diameters (defined by Response Evaluation Criteria in Solid Tumors 1.1), progression-free survival, and overall survival using Wilcoxon, Man-Whitney, Kaplan-Meier, and log rank statistics, as appropriate.

Results: All 69 patients have undergone a baseline DCE-CT scan. Of these, 59 patients have undergone DCE-CT scans at weeks 5 and 10; 5 patients

have a DCE-CT scan at week 5; and one patient has a DCE-CT scan at week 10. These DCE-CT scans are being analyzed at present.

Conclusion: Results and conclusions from this analysis as well as their correlation to the clinical endpoints will be presented.

- CH.41      Michał      INTEGRATIVE METHOD FOR ANALYSIS OF CANCER TRANSCRIPTOME AND  
                 Świtnicki      METHYLOME DATA IMPROVES IDENTIFICATION OF PERTURBED GENES  
                              AND SAMPLE CLASSIFICATION

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Cancer development is driven by a complex pattern of genomic and epigenomic perturbations. Mutations of genes and relevant regulatory elements are often reflected by changes in abundances of transcripts that ultimately cause abnormal cell behaviour. Another important element of cancer biology is the methylation of DNA at CpG sites, a mark that serves as a fingerprint of short-term epigenetic changes. Traditionally, independence is assumed when analysing multiple such signals, which is often not the case. For example, high gene body methylation increases transcript abundance via promoting transcription. What is more, such relationship is variable throughout the spectrum of methylation levels and also depends on other factors such as the physical distance between neighbouring CpG sites. High promoter methylation, however, may lead to a decrease of corresponding gene's expression level due to its insulating properties. Based on the interdependencies between DNA methylation and gene expression, we propose a method that can evaluate them along with their underlying biological relationship. Such an approach for integrative analysis has the potential not only to improve the discovery of relevant clinical biomarkers but also to more accurately classify clinical samples. Our method is highly flexible and, due to its modular nature of the elegant graphical models formalism, allows for inclusion of many other biological variables, which is especially relevant when they are known to be interdependent. We exemplify our approach by analysing a Breast Invasive Carcinoma cohort from The Cancer Genome Atlas consortium that includes 82 adjacent normal and 732 tumour samples.

- CH.42      Lea Hougaard      PET/MR AS A TOOL FOR IMAGING CHRONIC KIDNEY DISEASE  
                 Pedersen

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Chronic kidney disease is a common late-diabetic complication and the diagnosis is made from blood tests, 24-hours urine samples, or kidney biopsies. The purpose of this study is to investigate whether PET/MR imaging non-invasively can detect the grade of fibrosis in the kidneys.

which will help understand the disease progression and be an attractive alternative to monitoring treatment efficiency.

We use a transgenic mouse model for chronic kidney disease, which slowly develops thickening of the glomerular basement membrane, deposition of mesangial matrix and interstitial fibrosis, and reduced GFR.

The mice are injected i.v. with C<sup>11</sup> - labelled Metformin (n=5) and scanned for 90 min on a Mediso nanoScan PET/MRI scanner and compared to wildtype Balb/CA mice (n=5). A T2 weighted intrinsic tissue characterization optimized for kidney visualization is done after the PET recording and the kidneys are perfusion fixated. Renal fibrosis is identified on high resolution anatomical scans, and the relevant diffusion MRI derived metrics from these data sets are calculated.

The renal cortex shows highest radioactivity concentration 2 minutes after i.v. injection in both wildtype and transgenic mice, while renal medulla peaks later but has slower washout.

A region of interest is defined in the kidney parenchyma and the absorption is calculated as a function of time after i.v. injection. The transgenic mice shows significant delayed signal, which could indicate reduced perfusion in the kidneys in the transgenic mice compared to the wildtypes.

In conclusion, these results show that it is possible to use PET/MR scanning to detect differences in the kidneys between the two strains of mice.

CH.43 Moslem  
Ranjbar

#### ROLES OF MICRO-RNAS IN DIFFUSE LARGE B-CELL LYMPHOMA AND DRUG RESISTANCE

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MicroRNAs (miRNAs), a subclass of non-coding RNAs, function in gene regulation through mRNA degradation or direct inhibition of translation. miRNAs assist in regulating most cellular processes and are involved in development of a wide range of diseases. Yet, effects of miRNA in cancer development remain to be unveiled. Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin Lymphoma in adults with low survival rate due to drug resistance. In the present study, we are addressing the involvement of miRNAs in gene regulation and mechanisms of drug resistance in cancerous B cells.

We evaluated the expression level of different miRNAs in drug-sensitive and/or -resistant cell lines to define the main miRNA candidates involved in drug sensitivity. Our established lentiviral toolbox enabled us to manipulate the selected miRNA expression in cancerous B cell lines. We evaluated the drug response and proliferation of transduced and fixed cells using BrdU cell proliferation assays. Also, apoptosis rates were

evaluated by measuring PARP cleavage.

We showed that the lentiviral vector transduction significantly enhanced the resistance of cancerous B cell lines to Rituximab, demonstrating a strong anti-apoptotic effect of lentiviral transduction. Interestingly, miRNA-21, despite increasing the proliferation rate, decreases the resistance to rituximab. Similarly, miRNA 23a cluster decreases the resistancy to Doxorubicin. These data suggest that DLBCL miRNA profiles may have prognostic applicability and that miRNAs and/or miRNA inhibitors are potential candidates to be used alone or in combination with other drugs to increase drug efficacy and reduce resistance.

CH.44  
Camilla  
Hoffmann  
Merrild

#### SOCIAL INEQUALITY IN CANCER SURVIVAL. EXPLORING HEALTH CARE SEEKING PRACTICES IN DIFFERENT SOCIAL CLASSES

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Social inequality in cancer survival is well established. Research has suggested that this may partly be caused by differences in healthcare seeking, which has primarily been related with attitudes, knowledge and symptom awareness. Accordingly, the embodiment of social class and how it moves actors differently has largely been left unexplored. We seek to understand how people from different social classes are moved to seek help for health related concerns, by analyzing the different health care seeking practices in two diverse social classes.

Based on findings from long-term ethnographic fieldwork, we suggest that health care seeking practices of people from higher social classes often resemble consumerism, where the goal is to maximize the functional capacity. In the lower social classes, social suffering informed by the wider economic and social constraints and hardship, appears to inspire the way in which health care seeking is practiced. We illustrate how these different health care seeking practices correspond diversely with current forms of medical thinking, materialized in pro-active discourses of early diagnosis and the organization of medical practice, as exemplified in Danish general practice.

Overall, the presentation discusses how the sometimes diffuse and complex forms of social suffering of lower social classes are difficult to accommodate within the health care system, whereas the direct and specific forms of health care seeking manifested in higher social classes are encouraged.

CH.45  
Cathrine  
Carlsen Bach

#### PLASMA PERFLUOROALKYL ACIDS AND TIME TO PREGNANCY IN WOMEN FROM THE DANISH NATIONAL BIRTH COHORT REVISITED

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**Background:** The association between exposure to perfluorooctane sulfonate (PFOS) or perfluorooctanoate (PFOA) and the time to pregnancy has been investigated in women in a few studies with conflicting results. In this study, we aimed to expand our previous findings by using a different subsample from the same cohort and to perform pooled analyses of the two subsamples.

**Methods:** From participants in the Danish National Birth Cohort, we selected two samples of women. We measured the concentrations of PFOS and PFOA by liquid chromatography-tandem mass spectrometry in plasma obtained during pregnancy. The women reported their time to pregnancy at approximately 12 weeks of gestation. In the pooled sample, and separately for the two subsamples, we used a discrete-time survival model to estimate adjusted fecundability ratios and multiple logistic regression to estimate infertility odds ratios.

**Results:** In the pooled analyses, fecundability ratios were decreased by 13–22% for the three higher quartiles of PFOS or PFOA compared to the lowest. For sample 1 (n=1161), the estimates were slightly lower, but for sample 2 (n=440), PFOS and PFOA were not clearly associated with decreased fecundability ratios. Infertility odds ratios were higher with exposure to PFOS or PFOA in sample 1 and the pooled sample, but no clear pattern was evident for sample 2.

**Conclusions:** We found different results in two subsamples from the same cohort. The results from the new sample did not corroborate the association in our older sample from a previous study. The new sample was smaller, but these results are in line with most of the existing literature.

CH.46      Mette  
              Kjærgaard  
              Nielsen

#### FAMILY CAREGIVERS OF TERMINALLY ILL PATIENTS. WHO ARE THEY?

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**Introduction:** Family caregivers of terminally ill patients are in a vulnerable position. They have an increased risk of psychological distress in terms of depression, pre-loss grief and caregiver burden. Further, behavioral factors such as caregivers' communication with the patient about illness and death and preparedness of the impending death have an impact on caregivers' well-being. Large-scale studies on the frequency of these factors and their impact on caregivers are lacking.

**Aim:** This study aims to investigate caregivers' 1) extent of psychological distress (depression, pre-loss grief and caregiver burden) and 2) their

communication with the patient about illness and death and their preparedness of the risk of losing the patient.

Method: In 2012, all Danish patients granted drug reimbursement in connection with terminally illness were asked to pass on a questionnaire to their closest relative.

Results: 3,637 caregivers returned a questionnaire (38% of the 9,512 patients approached). Of the caregiver cohort, 17% suffered from depression, 12% had pre-loss grief and 12% experienced moderate-severe caregiver burden. The proportion of caregivers rating their communication about illness and death low was as low as 46%, and 13% felt unprepared for the risk of losing the patient to the illness.

Conclusion: A considerable proportion of caregivers of terminally ill patients are experiencing psychological distress, low levels of communication and low preparedness. Health professionals should be aware of potentially modifiable factors affecting family caregivers and support caregivers' and patients' communication about illness and death and increase caregivers' preparedness.

CH.47 Peter  
Bondeven

#### IMPACT OF THE LENGTH OF REMNANT RECTUM ON BOWEL FUNCTION AFTER SPHINCTER-PRESERVING SURGERY FOR RECTAL CANCER

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Background: The combination of the advances in surgical technique and neoadjuvant therapy has resulted in more patients having restoration of bowel continuity by sphincter-preserving surgery. Unfortunately, numerous patients experience anorectal dysfunction following resection of the rectum, often referred to as low anterior resection syndrome (LARS), and many suffer lifelong severe disability with a major impact on quality of life.

Aim: The aim of this study was to investigate the impact of the length of remnant rectum, determined by postoperative MRI of the pelvis, on bowel function.

Methods: A total of 115 patients with sphincter-preserving surgery for rectal cancer were studied. Postoperative bowel function was assessed and postoperative MRI of the pelvis was performed within a minimum of one year following surgery. Bowel function was assessed using the LARS score, and the length of remnant rectum measured on postoperative MRI.

Results: Overall, major LARS was observed in 37% of patients. The ordinal length of remnant rectum was significantly associated with the risk of having major LARS ( $P < 0.0001$ ). The risk of major LARS was more than 70% when less than 2 cm of remnant rectum was preserved. Only two patients with more than 6 cm of remnant rectum reported having major LARS, and both of these had received preoperative radiotherapy. Preoperative radiotherapy was an independent risk factor for major LARS, irregardless of

remnant rectum length (OR: 3.5, 95% CI: 1.15-10.4).

Conclusion: Length of remnant rectum after sphincter-preserving surgery for rectal cancer had a major impact on bowel function.

- CH.48 Sebastian Ranzi Kotze LOW-GRADE INFLAMMATION IS ASSOCIATED WITH LOWER HAEMOGLOBIN LEVELS IN DANISH BLOOD DONORS: RESULTS FROM THE DANISH BLOOD DONOR STUDY

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Background: Chronic inflammation can lead to anaemia of chronic disease, partly due to the sequestration of iron caused by inflammatory cytokines and the protein hepcidin. However, the effect of low-grade inflammation (LGI) on haemoglobin (Hb) levels among healthy individuals is not known. The aim was to study the effect of LGI on Hb among Danish blood donors.

Methods: The Danish Blood Donor Study is a nationwide study and bio-bank. We performed multivariable linear regression to assess the effect of LGI (high-sensitivity C-reactive protein over 3mg/L) on Hb in 9,136 men and 8,092 women. We adjusted for donation activity, and physiological and lifestyle factors. We also performed multivariable logistic regression to evaluate the effect of LGI on the risk of having low Hb (below the 10<sup>th</sup> percentile among men and women, respectively). All analyses were stratified for sex and smoking status.

Results: We found a negative association between LGI and Hb in non-smokers (men:coef.=-0.075mmol/L, p<0.001; women:coef.=-0.097mmol/L, p<0.001). There was a positive association between LGI and Hb among smoking men (coef.=0.207mmol/L, p<0.001) and a tendency towards a positive association among smoking women (coef.=0.065mmol/L, p=0.074). LGI was also associated with an increased risk of having low Hb in non-smoking women (OR=1.43, p=0.001).

Conclusions: LGI was negatively associated with Hb levels among non-smokers, presumably via the protein hepcidin. LGI was positively associated with Hb among smokers, probably because smoking leads to increased inflammation as well as increased Hb levels through CO exposure. LGI was also associated with an increased risk of low Hb in non-smoking women.

- CH.49 Kathrine Hansen TURNOVER OF THE STING PROTEIN AND IMPACT ON THE TYPE I IFN RESPONSE

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The sensing of nucleic acids in the cytoplasm is important for the host response to several pathogens. Upon detection of dsDNA derived from bacteria or virus by the cytosolic sensor cGAS, cGAS catalyses the



production of the cyclic-dinucleotide, cGAMP from ATP and GTP. cGAMP bind to the adaptor protein STING, which serves as a platform for downstream signaling events leading to type I IFN production. In the recent years, STING has emerged as a key molecule for innate immunological function.

We identified the ubiquitin binding protein, p62, which is known to target ubiquitinated proteins for autophagy, to be important for the protein level of STING. p62 was found to colocalize with STING in MEF cells by confocal microscopy. Furthermore, p62 knockout MEFs expressed a constitutive higher level of STING as determined by western blotting. This was also observed in ATG5 knockout MEFs, indicating constitutive degradation of STING by autophagy.

Interestingly dsDNA-induced degradation of STING was observed in wildtype MEFs as well as p62 knockout MEFs, indicating an autophagy-independent degradation pathway. Proteasomal degradation of STING has been shown following stimulation with sendai virus, and further experiments will show if this is a general mechanism to control excessive antiviral innate immune response upon sensing of nucleic acids.

In conclusion, the regulation of the STING protein level seems to be a complex interplay between constitutive, autophagosomal and proteasomal degradation. This will in turn result in a tight regulation of the type I IFN response upon sensing of nucleic acids.

CH.50 Thomas Nordstrøm Kjær

#### RESVERATROL AMELIORATES IMIQUIMOD-INDUCED PSORIASIS-LIKE SKIN INFLAMMATION

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Background: The polyphenol Resveratrol (RSV) has anti-inflammatory effects in various settings of low-grade inflammation; therefore, we investigated whether oral RSV treatment has anti-psoriatic effects in an Imiquimod (IMQ)-induced psoriasis-like mouse model.

Objective: To assess the effects of oral RSV treatment of psoriasis-like skin inflammation in mice.

Method: The study was comprised of three groups treated with: Vehicle cream (control group), IMQ cream (IMQ group), IMQ cream+RSV (IMQ-RSV group). Psoriasis severity was assessed using elements of the Psoriasis Area Severity Index, direct skin thickness measurements and histological examination.

Results: IMQ treatment induced a psoriasis-like skin inflammation as seen by skin thickening, redness and scaling. However, RSV significantly diminished the severity of the psoriasis-like skin inflammation. Gene

expression in skin was analysed using RNA microarray and qPCR. RNA microarray found psoriasis-like changes in the gene expression-profile of IMQ group and revealed significant RSV mediated changes in several relevant genes, like increased expression of genes associated with retinoic acid stimulation and reduced expression of IL-17 dependent pathways and IL-17A.

Conclusion: RSV ameliorates the IMQ-induced psoriasis-like skin inflammation, and we suggest the effects are mediated via retinoic acid and IL-17 dependent pathways. Our results suggest that RSV could be a new option in the treatment of psoriasis and should be tested in a human setting.

CH.51      Esben      THE PATTERN-RECOGNITION MOLECULE MANNAN-BINDING LECTIN (MBL)  
Axelgaard      IN THE PATHOPHYSIOLOGY OF DIABETIC NEPHROPATHY

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The complement system is part of the innate immune system and is an important part of the first line of defence against pathogens. Mannan-binding lectin (MBL) is one of the pattern- recognition molecules that may initiate the lectin pathway of complement activation. As opposed to obvious evolutionary beneficial effects of the complement system, MBL is associated with adverse effects in several diseases including diabetes. There is evidence that link MBL to poor prognosis for the kidney in diabetes. The precise mechanism of linkage between the complement system and diabetic nephropathy remain poorly elucidated. Two putative mechanisms are proposed: 1) the formation of neoepitopes for MBL pattern recognition on host cells would enable lectin pathway activation, and 2) inactivation of complement regulatory proteins by glycation that may exaggerate complement attack on host cells. MBL initiates the lectin pathway through binding to carbohydrates of both specific type and density, which thus provides sufficient binding avidity. The character of MBL binding-sites on host cells remains unknown, but it is speculated that altered protein glycation in diabetes permits MBL binding. Based on new studies using MBL/double knockout C57bl/6j mice, we present new evidence supporting the notion that MBL may indeed be involved in the pathophysiology of diabetic complications. Using the in vivo pre-clinical imaging system (IVIS Spectrum), we show that diabetic mice, as compared to non-diabetic MBL/double knockout C57bl/6j mice, exhibit a larger degree of accumulation of intravenous administered MBL in specific organs.

CH.52      Gitte Julie      ANTAGONISM AMONG STAPHYLOCOCCUS EPIDERMIDIS AND  
Christensen      PROPIONIBACTERIUM ACNES ISOLATED FROM HEALTHY AND ACNE  
AFFECTED HUMAN SKIN

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The aim of this study was to highlight the presence of antagonistic interactions between the two abundant skin colonizers *S. epidermidis* and *P. acnes*, and to determine the potential significance of bacterial interferences in the pathogenesis of acne vulgaris. 75 *S. epidermidis* isolates from healthy and acne-affected skin were examined for inhibitory activity against representatives of 58 *P. acnes* strains, representing individual evolutionary lineages, isolated from acne, healthy skin, and systemic infections. The screening was carried out as a simultaneous antagonism assay. All 75 *S. epidermidis* strains exhibited inhibitory activity against *P. acnes* to some degree. A subgroup of genetically closely related *P. acnes* strains isolated from patients with severe acne was significantly less susceptible to the staphylococcal antimicrobial activity than other strains. This suggests that such interspecies interactions may play a role in jeopardizing normal balances in the skin microbiota, leading to a dysbiosis. Staphylococcal antimicrobial compounds might therefore play an important role in maintaining a healthy normal flora on the human skin thus contributing to resistance to acne disease.

A second aim of this study was to isolate and characterize an antimicrobial compound with a broad antimicrobial activity against nearly all *P. acnes* strains. This broad, but yet species-specific compound, may be used as a protective agent against *P. acnes*, and hence as a potential treatment option against acne or other *P. acnes*-associated diseases.

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